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OPHTHALMOLOGY

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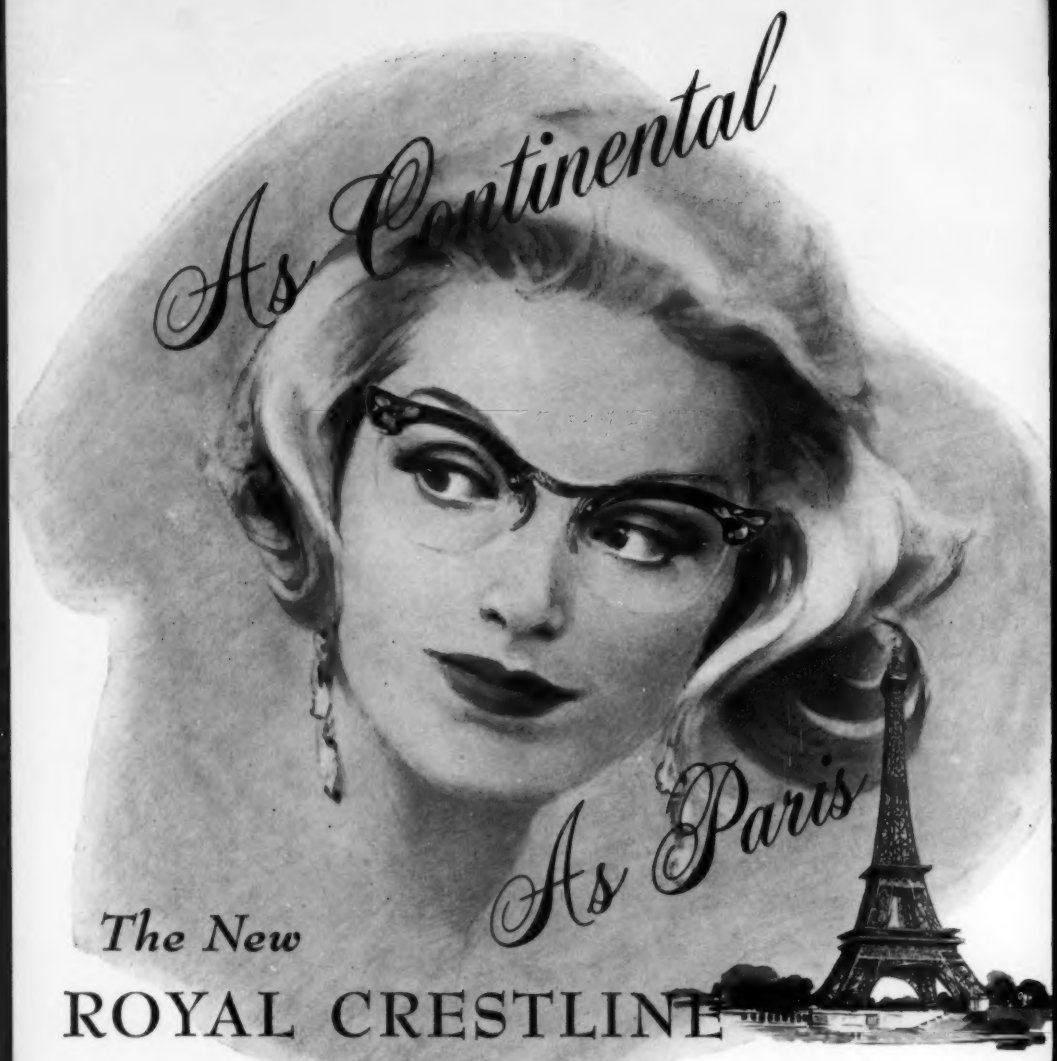

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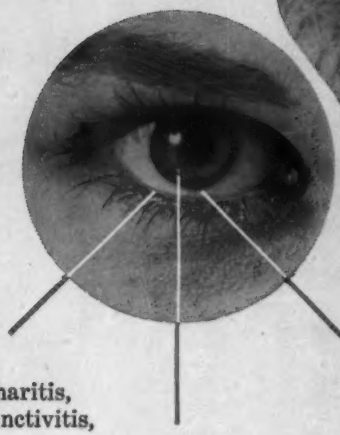

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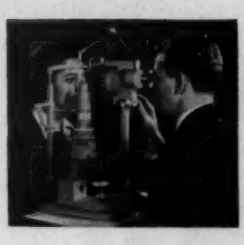

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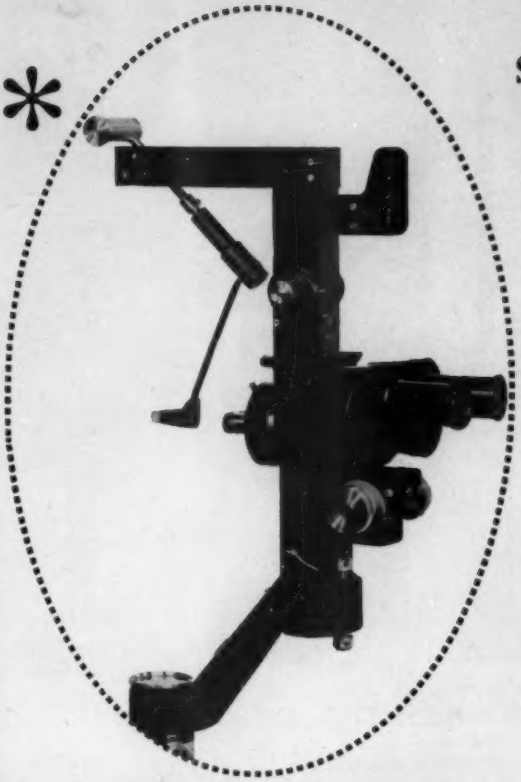

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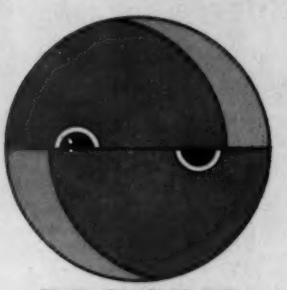

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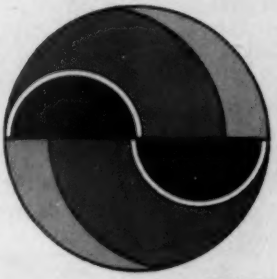

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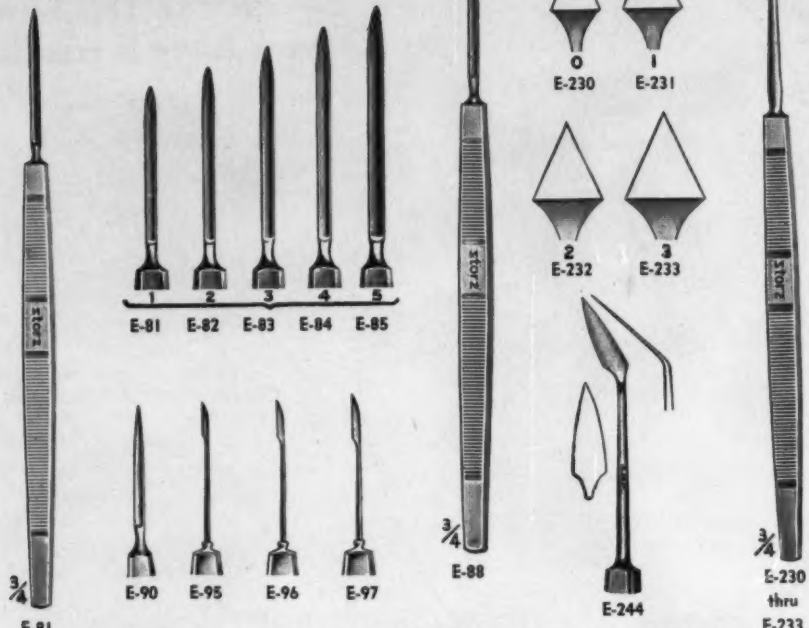

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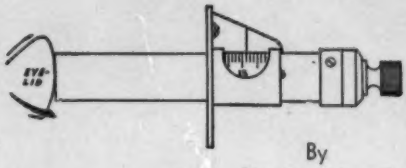

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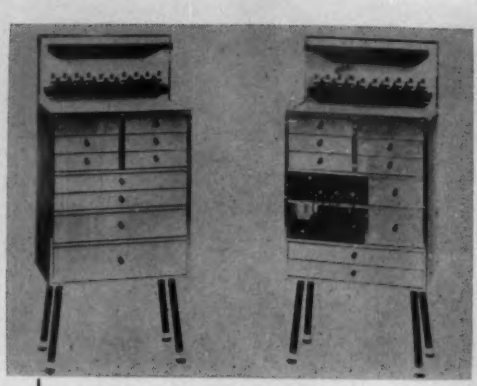

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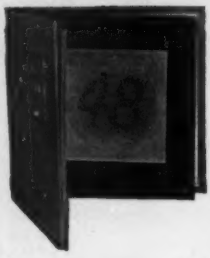

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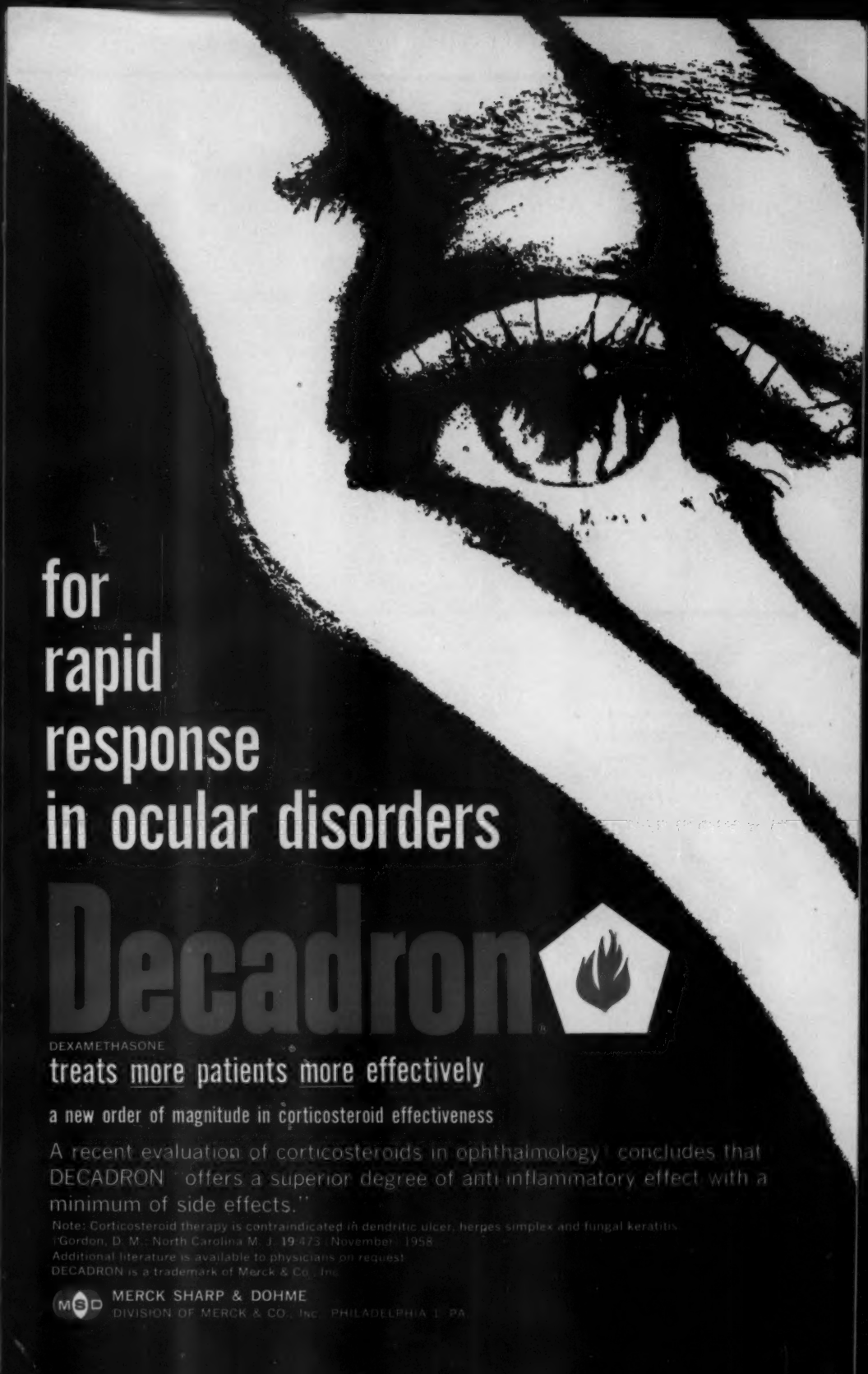
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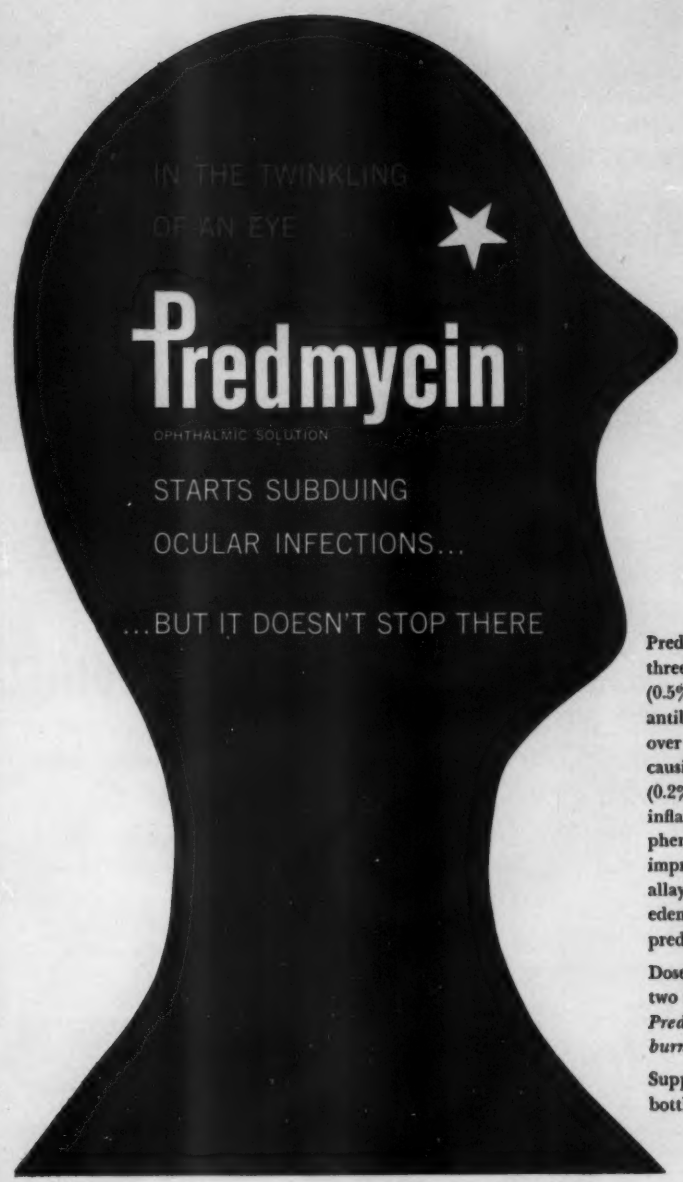

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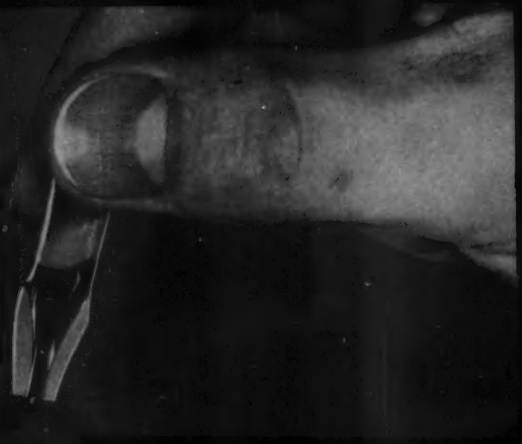

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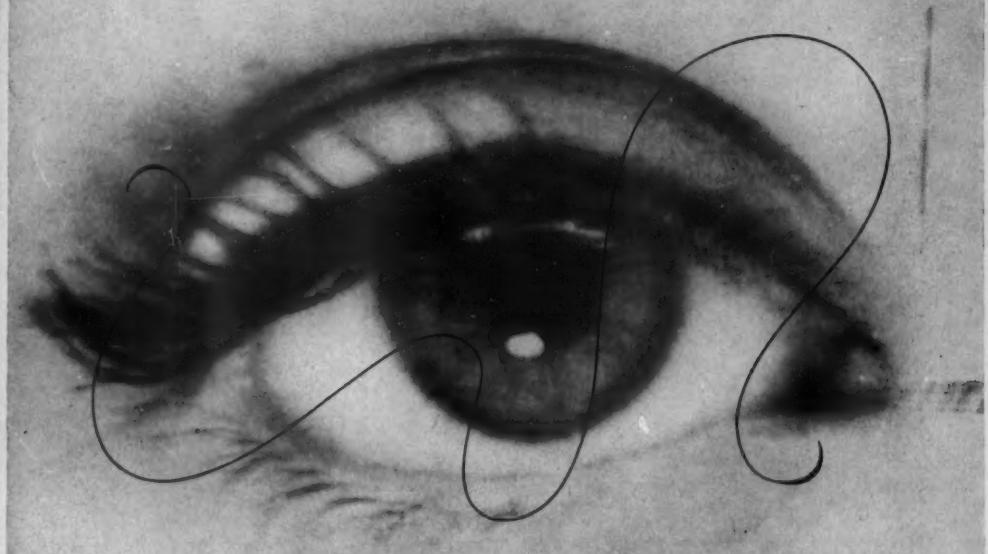

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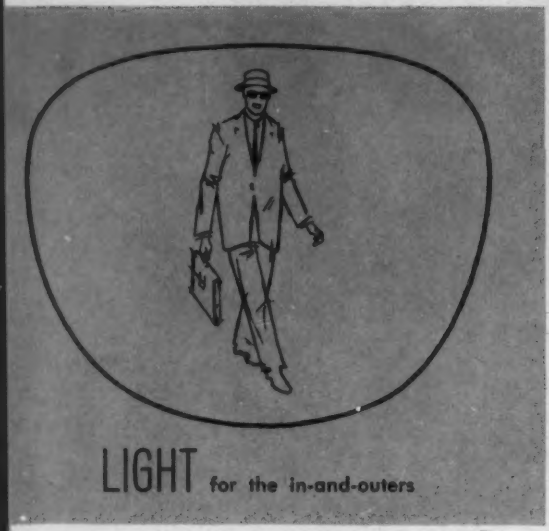

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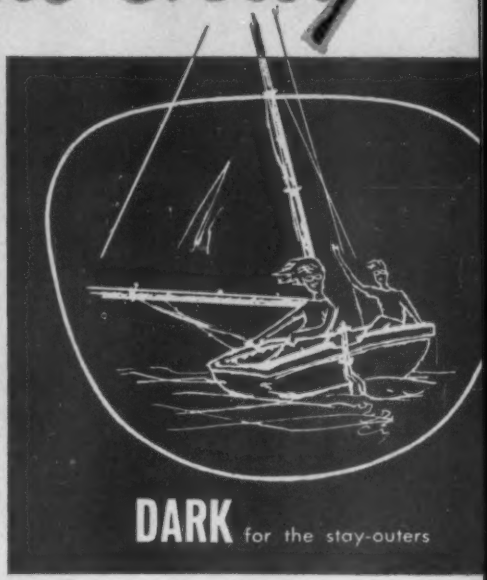

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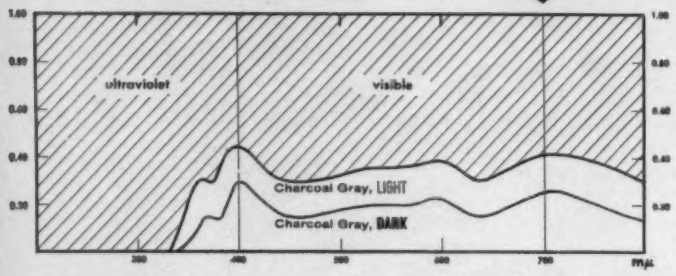

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Fundal Changes Resembling Colloid Bodies in Recurrent Polyserositis (Periodic Disease)

I. MICHAELSON, M.D.; M. ELIAKIM, M.D.; E. N. EHRENFELD, M.D., and M. RACHMILEWITZ, M.D., Jerusalem

In 1946, two of us (M. R. and E. N. E.) first observed a clinical syndrome which consisted of paroxysms of fever accompanied by abdominal and chest pain due to inflammation of the peritoneum and the pleura. The condition was then described as "recurrent benign polyserositis." At about the same time and subsequently a similar clinical picture was detailed by Siegal (1945, 1949), under the heading of "benign paroxysmal peritonitis," and by others, under various designations (Mamou and Cattan, 1952; Schapiro and Treinin, 1953; Heller, Kariv, Sherf, and Zohar, 1955; Rachmilewitz, Ehrenfeld, and Eliakim, 1958). Reimann (1948) first used the name of "periodic disease" which has been widely accepted. However, in the original and in subsequent reports Reimann included a variety of recurrent disorders with different clinical manifestations. Recently this condition was extensively reviewed by Mamou (1956). The prevalence of recurrent polyserositis among people from Mediterranean countries has been stressed.

Routine funduscopic examinations performed during the last year on patients with recurrent polyserosisis disclosed fundal changes resembling colloid bodies in a percentage which warranted a further study of a larger number of patients. The fundal findings were first briefly reported in 1957 (Rachmilewitz, Ehrenfeld, Eliakim, and Michaelson). This report deals with 23 patients with recurrent polyserositis, with particular reference to their fundal findings.

Submitted for publication Nov. 22, 1958.

From the Departments of Ophthalmology and Internal Medicine "B," Rothschild Hadassah University Hospital.

Clinical Observations

All patients exhibited the typical paroxysms of fever and diffuse abdominal and, frequently, chest pain; swelling and pain of one or more joints occasionally accompanied the attack, which usually lasted 24 to 48 hours. Transient leukocytosis and increased sedimentation rate were found during attacks. One patient had albuminuria. The attacks occurred at either regular or irregular intervals of several days to weeks. Spontaneous remissions lasting from several months to two years were recorded. In the intervals between attacks most patients felt well and were able to carry on with their work. The general health of the patients remained unimpaired, even in those in whom the disease lasted more than 20 years.

Fourteen of the patients were male and nine female. The age at onset of the disease ranged from 6 to 36 years, the average being 19. All patients were Jews, 21 of Sephardic or oriental parentage and two Ashkenazim.*

* Ashkenazi Jews are those coming from Europe, America, Australia, and South Africa. Orientals hail from various Middle Eastern and North African countries, while Sephardic Jews are those whose ancestors left Spain in the 15th century and dispersed over various Middle Eastern and European countries.

TABLE 1.—*Incidence of Colloid Bodies in Twenty-Three Cases of Recurrent Polyserositis*

	No. Cases	%	Av. Age at Examination, Yr. *	Av. Duration of Disease, Yr. *
Many	8	34	32 (19-46)	16 (4-30)
Few	5	22	36 (29-45)	12 (4-25)
None	10	44	27 (13-50)	11 (6-28)

* Range indicated in parentheses.

Occurrence of the disease in more than one member of the family was found in three instances.

Funduscopic Findings

Dotted lesions in the fundus of the eye were found in 13 out of the 23 patients (56%) (Table 1). On slit-lamp examination these lesions were localized in the lamina of Bruch and are, therefore, considered to be colloid bodies. The dots, which varied in size from 70μ to 300μ, were porcelain white or yellowish in color. In most cases the dots had a punched-out appearance, while in others the margin was less well defined and pigmented. The dots were often arranged in rows, assuming a quasigeometric distribution suggestive of domino appearance. In eight of the cases (34%) the dotted foci were numerous and widespread, while in the remaining five cases only two or three isolated foci were found. The lesions were found in both eyes.

The patients showing fundal changes were followed for as much as six months, during which, in most cases, there did not appear any notable changes. However, in two cases it was possible to observe the evolution of the fundal changes. The initial porcelain white punched-out appearance of the bodies could be seen to give way to a yellowish-white tint with a less defined margin, often pigmented. In places the dot became entirely pigmented. A marked increase in the number of the foci could also be observed. This evolution, unusual for colloid bodies associated with advanced age, was observed in a case from which Figure 1 was taken. Occasionally the focus might be as large as about one-third of the disc (Fig. 2).

Fig. 1.—Appearance of fundus showing evolution of changes. The number of colliod bodies increased within a short time.

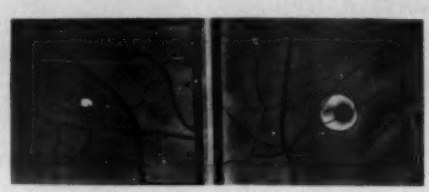

Fig. 2.—These figures were taken from one fundus. They illustrate the variations in size of the colloid bodies.

There was a further case of recurrent polyserositis, not included in this series of 23 cases, which presented the unusual fundal appearance shown in Figure 3. A solid-looking mulberry-like mass, the size of about one-third of the disc, lay on the surface of the retina in the upper part of the fundus. A short distance above the mass was a small focus of retinochoroidal scarring which probably represented its original situation. The mass had the typical appearance of a colloid body of the optic disc. The case is not included in the series

Fig. 3.—An unusual change noted in a case of recurrent polyserositis.

because of the difficulty of interpreting the fundal findings.

The general description given above applies to all 13 cases in which fundal changes were present. No abnormal findings excepting those mentioned were noted. In the remaining 10 cases of this series no abnormal changes were present in the fundus.

The average age of the patients belonging to the group with positive eye findings was somewhat higher than that of the patients with no fundal findings (Table 1). The average duration of the disease in both groups at the time of the fundal examination did not differ significantly, although it seemed that patients with numerous colloid bodies had a longer average duration. There were patients suffering from the disease for four years who exhibited numerous colloid bodies in the fundi, while one patient who had the disease for 28 years showed no changes at all.

Control Series

Because of the frequent occurrence of colloid bodies in persons above the age of 50, it was considered advisable to establish their incidence in a control group. Two hundred thirty-two patients visiting the Ophthalmic Outpatient Department were used for this purpose, no selection being made except to exclude cases with fundal findings which might explain the presence of colloid bodies. An analysis of this group is given in Table 2. It can be seen that 11% of the cases had colloid bodies, but only in 4% were they numerous, as compared to 34% of the recurrent polyserositis group (Table 1). The average age of the control-group patients showing numerous colloid bodies was 40 years, as compared to 32 years in the recurrent polyserositis group. It is of interest that the 206 control cases who had no colloid bodies had an average age of 32. Further analysis of the control-group cases with numerous colloid bodies (nine cases, or 4%) showed that one patient had lupus erythematosus disseminatus, one migraine, one necrobiosis lipoidica, and one malignant exophthalmos with thyrotoxicosis. It is possible that age and accompanying diseases may have been factors in the 4% incidence of numerous colloid bodies in the control cases.

TABLE 2.—*Incidence of Colloid Bodies in 232 Control Cases*

	No. Cases	%	Av. Age at Examination, Yr. *
Many	9	4	40 (20-55)
Few	17	7	40 (8-67)
None	206	89	32 (12-52)

* Range indicated in parentheses.

Comment

The presence of fundal lesions resembling colloid bodies in 56% of patients with recurrent polyserositis seems highly significant in view of the findings in the control series. It is apparent that this high incidence is not explicable by senility or the presence of other fundal diseases.

The known pathological conditions of the lamina of Bruch which give rise to clinical and histological changes are as follows: colloid bodies in the cuticular layer associated with advanced age; ruptures of the elastic portion of the membrane—angioid streaks; ruptures of the membrane through both its layers—disciform degeneration of the retina. Little or nothing is known of the etiology of these changes in Bruch's membrane. Of general conditions associated with pathology in Bruch's membrane only one is known—the Groenblad-Strandberg syndrome, in which changes in the elastic tissue of the skin, the blood vessels, and the elastic layer of Bruch's membrane are found. It is therefore of interest that in recurrent polyserositis lesions resembling colloid bodies appear more frequently than they do in normal persons. Furthermore, as previously mentioned, one of the patients in the control group, who had numerous colloid bodies, suffered from necrobiosis lipoidica, a disease affecting the elastic and connective tissues of the skin. Another control patient had disseminated lupus

erythematosus, a disease of connective tissue frequently accompanied by polyserositis.

Too little is known of the etiology and pathogenesis of recurrent polyserositis to enable a suggestion to be made regarding the mechanism whereby the lesions described are produced, nor does this local eye pathology apparently throw any light on the general pathology of recurrent polyserositis. It must be stressed that in the cases studied by us, no evidence of amyloidosis or general vascular disease was present. It must suffice at present to note the clinical concurrence of colloid-body-like lesions and recurrent polyserositis and to note that to the Groenblad-Strandberg syndrome must be added another general dyscrasia that may cause changes in the lamina of Bruch.

Summary

The presence of fundal changes resembling colloid bodies is described in 13 (56%) out of 23 cases with recurrent polyserositis. In eigth cases (34%) with an average age of 32 years the lesions were numerous and widespread, while in five cases (22%) with an average age of 36 years they were few and isolated. Of a control group of 232 cases, 4% were found to have numerous and 7%, few colloid bodies. Higher age (average 40 years) and accompanying diseases may have contributed to the 4% incidence in the control group.

Because of their frequent appearance, the fundal lesion described may be regarded as one of the signs of recurrent polyserositis.

M. Ivry prepared the illustrations.

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Exudative Type of Retinal Separation

A Case of Harada's Disease in an Eight-Year-Old

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Harada's disease [1] is rarely seen in America, and of those cases reported by Cordes,[2] the majority were in persons from highly pigmented races and all were in adults. The following case is reported in detail because it is unique in the age of onset and in severity of symptoms. The progress of the case over a four-year period, as well as the response to oral steroid therapy, will be described.

An 8½-year-old white girl developed a severe cold with fever and coughing. At the onset her parents noted some redness of the eyes and possible swelling of the lids. The symptoms of the cold subsided one week later, but the patient noted some photophobia and blurring of vision. Over the next week vision progressively diminished to the point where school work became impossible, and the patient saw large "bubbles" in front of her eyes. Her pediatrician was consulted, and he reported her physical condition as normal. A routine chest x-ray and blood cell count were normal. She was referred at that time to an ophthalmologist.

Family history was noncontributory. Her father was of Irish and her mother of French origin. There was no family history of eye disease. The child had had a normal, full-term birth. She had received the usual diphtheria, tetanus, and typhoid immunizations but no polio vaccine. Her only childhood diseases were rubeola at the age of 2 and varicella at the age of 7 years. Figure 1*A* shows the child at the age of 7.

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From the service of Dr. Paul Chandler, Massachusetts Eye and Ear Infirmary, with the help of Dr. Alan Butler and Dr. K. K. Kimura of the Department of Pediatrics of the Massachusetts General Hospital and Harvard Medical School.

When first seen by an ophthalmologist, three weeks after the initial cold symptoms, the patient presented the following ocular findings: vision was reduced to hand movements, and there was slight edema of both lids and minimal ciliary injection. Numerous coarse k. p.'s were seen on the corneal endothelium. There was a strong ray and myriads of cells in the anterior chamber. Triangular-shaped deposits of cells were seen on the lens capsule, and some posterior synechiae were forming. There were numerous coarse and fine vitreous opacities. Tension was 6 with a 5.5 wgt. Schiøtz.

The fundus reflex was yellowish with a poor reflex below. The retina was wholly detached with large bullae below. There were fine yellowish intraretinal exudates. The vessels at the disc margin were dilated. No retinal tears were detected. Figure 1*B* shows the appearance of the child at this time, and Figure 2 shows her fundus.

The patient was hospitalized. Physical examination was unremarkable except for the eyes. Laboratory tests revealed normal blood proteins, N. P. N., cholesterol, sugar, and glucose tests. Tuberculin test was negative to 1:100 dilution. Nose, throat, and virus cultures were unremarkable. There were normal chest, skull, and spine x-rays and a normal audiogram. A lumbar puncture was performed and revealed a slightly elevated initial pressure. Total cells were 93 per cubic millimeter. All cells appeared to be lymphocytes. Protein was 30 mg. %, and sugar was 58 mg. %. Colloidal gold curve recorded as 0122100000. The eosinophil count was 68.

Figure 1

Initial therapy consisted of 2.5% hydrocortisone and 1% scopolamine drops locally at frequent intervals. The patient was given 75 mg. prednisone (Meticorten) orally for the first three days, after which the dose was gradually reduced to a maintenance level of 30 mg. daily at the end of the first month.

Her weight at the beginning of therapy was 56½ lb. After two weeks of therapy the patient noted subjective improvement in vision, which was measured at 15/200. There was a rapid clearing of the ocular media and absorption of the subretinal exudate.

Figure 1*C* shows incipient moon facies after one month of therapy. At this time the child's weight was 68 lb., and her general physical condition was unchanged. Blood pressure was 112/60.

The eosinophil count varied from zero to nine, and a repeat lumbar puncture showed marked reduction in cells.

Her vision was 20/70 with correction. External examination revealed slight edema of the lids associated with facial edema. There were occasional white eyebrows, and patches of white hair were noted on the patient's scalp for the first time. The ocular tension had increased to normal levels.

Figure 2

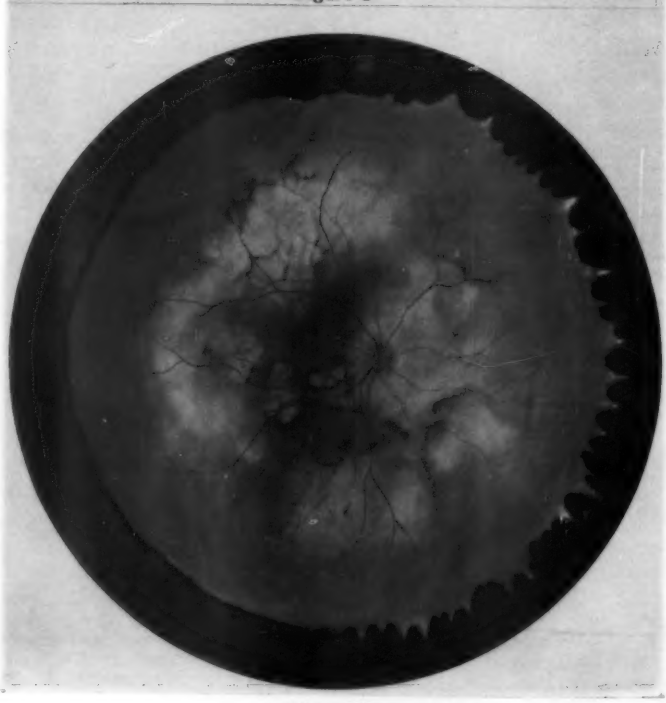

Figure 4

There was still a 2+ flare and cells in the anterior chamber and some posterior synechiae forming. The pupil was well dilated by the scopolamine. The fundus showed the retina to be in position with patches of dark pigmentation corresponding to the areas of choroiditis depicted in Figure 2. Treatment with local medication continued as described, and oral prednisone was maintained at the level of 20 mg. a day for the next month.

Figure 1*D* shows the appearance of the patient two months after the onset of the disease (age 8 years 8 months). Her weight was then 75 lb. Her general physical appearance showed marked basophiloid changes with facial and body hirsutism. Eosinophil count was 20.

Her vision was 20/40 with correction. There was marked poliosis of eyelids and eyebrows. On one finding tension was elevated to 30 mm. There remained a 1+ flare and 2+ cells in both eyes, with persistent multiple vitreous opacities. The fundus showed marked increase in pigmentation and suggested somewhat the appearance of congenital grouped pigmentation. The prednisone dose was reduced to 10 mg. per day.

Three months later, the patient noted increased blurring of vision and the eyes appeared congested. She was examined and found to have diminished vision with an increase in cells and flare and increased vitreous opacities. The dose of prednisone was accordingly increased to 50 mg. per day, which produced marked improvement in vision and in transparency of the ocular media.

Figure 1*E* shows the patient six months after onset of the disease (age 9 years 2 months). She then weighed 87 lb. There was marked bull-neck, hirsutism, obesity, and Cushing facies. Blood pressure was 116/85. X-rays revealed some osteoporosis.

Vision was 20/40 with correction. The poliosis of lids persisted, and the anterior chamber showed 1+ flare and cells. Tension was normal, and the media were clearer than in the previous examinations. The fundus showed noticeable atrophy of the choroid. Prednisone was again reduced to 20 mg. per day, with continuation of the local scopolamine and hydrocortisone drops. Potassium chloride tablets were added to the regimen.

Any attempt to reduce steroid therapy further was accompanied by a diminution in vision, making it impossible for the patient to do her school work. The resumption of adequate levels of oral steroids maintained sufficient clarity of the ocular media and the vision at approximately 20/40. One year after the institution of steroid therapy, oral cortisone was alternated with the prednisone because of the complicating osteoporosis. Despite the beneficial effect on visual acuity, chorioretinal atrophy continued to progress and the pa-

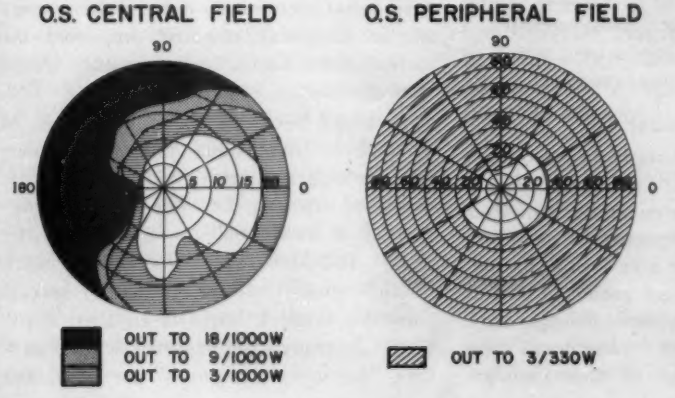

Figure 3

tient complained of the symptoms of night blindness.

Figure 1*F* shows the patient one and one-half years after first examination (age 10). At this time she was being maintained on oral prednisone alternated with oral cortisone. An additional course of typhoid therapy had been tried without dramatic results.

At this examination the patient's weight was approximately 75 lb. There was some diminution of the Cushing facies, with persistence of hirsutism. There was less osteoporosis noted in the x-rays. Central vision was 20/50 with correction, but there was a decrease in the visual fields as shown in Figure 3. Poliosis of lids persisted, but that of the scalp had diminished. There were occasional cells in the anterior chamber with a 1+ flare. Tension was normal with little change in the condition of the vitreous.

Figure 4 shows the appearance of the fundus at this time. There was marked chorioretinal atrophy, with a diminution in the amount of visible pigmentation compared to previous examinations. Only the posterior pole appeared spared from the degenerative process.

The patient was maintained on this oral steroid regimen from this point until the end of 1958. During this time the patient was taken to the National Institutes of Health Hospital in Bethesda, Md., where complete studies failed to detect a focal cause of her illness. Now, three years after the onset of the illness and the beginning of steroid therapy, the patient still has central vision in the left eye. Most recently, a secondary glaucoma has arisen which is being controlled by acetazolamide (Diamox).

Comment

Harada[1] first described this syndrome in 1926, and since that time fewer than 20 cases have been reported in the American literature. Cordes[2] reported in detail the results of treatment of a case in a 31-year-old Japanese woman and presented a thorough review of the literature through 1954. Since his article, a few[3,4] additional cases have been reported. Of all cases reported, most were in persons of highly pigmented races and all were in adults.

Kimura[5] summarized the experience of over 800 cases of uveitis in children without mentioning a case of this syndrome. It would appear, therefore, that the occurrence of an extreme form of exudative chorioretinitis in a child of this age is unique.

There does not appear to be any specific treatment for this condition. Cordes' case was not benefited by cortisone treatment, while in Bronstein's case,[3] as in ours, there was a symptomatic improvement with prednisone therapy and a relapse when the hormone was discontinued. With respect to the length of time with which patients have been treated with steroids, Crawford[6] reports a case of sympathetic ophthalmia apparently cured after more than four years' treatment with cortisone. Beneficial results with steroid therapy were observed in Harada's disease and allied conditions by Nano,[4] Bronstein,[3] and Forchheimer.[7] In the latter's case of sympathetic ophthalmia, topical steroids were successfully employed with a four-year follow-up. Offret[8] reviewed the results of five years' experience in uveitis treated with steroids and found, in general, that the chronic cases are resistant to treatment. In our case, however, there appears to be some beneficial effect even after three years. Although the hormone has failed to prevent progressive chorioretinal atrophy or to arrest the disease, it has successfully reduced the severity of the exudative response, improved the clarity of the media, and maintained useful central vision.

Redslob[9] reviewed the pathogenesis of sympathetic ophthalmia and the various theories suggested since the disease was first described. Among these theories, that suggesting a viral etiology is proposed by Ikui[10] and Malatesta,[11] whereas the work of Bullington,[12] as well as that of several Japanese workers, suggests an allergic etiology. In many cases reported in the literature, "meningeal symptoms" are noted, but

no cerebrospinal fluid findings are reported. Our patient had a lymphatic cerebrospinal fluid pleocytosis of 93. It would appear useful in every case of this or allied conditions to examine the spinal fluid and do viral studies early in the disease.

Solanes has by far the largest experience with the study of pathological material from the Vogt-Koyanagi-Harada and sympathetic group. For many years Solanes felt that Harada's disease and the Vogt-Koyanagi syndrome were nongranulomatous uveitis, while sympathetic ophthalmia has been viewed as a granulomatous uveitis. However, Solanes,[13] in a personal communication to me, said that he now feels that Vogt-Koyanagi syndrome is indeed a granulomatous uveitis. Hager[14] and Yuge[15] both find that the pathology of Vogt-Koyanagi syndrome is identical with sympathetic ophthalmia.

In the past decade it has become increasingly clear that Harada's disease, the Vogt-Koyanagi syndrome, and sympathetic ophthalmia are slightly different manifestations of a single disease. The Japanese ophthalmologists who were responsible for the original reports of two of these conditions have always felt this unity on the basis of clinical observations.

Dr. Mitsui[16] saw our patient early in the course of her disease and felt the prognosis to be favorable. He was surprised, however, by the youth of the patient. He made the following observation concerning the accessory skin signs in this syndrome. In every case the cephalad regions are the most strongly affected, whereas skin or hair changes at the caudal end of the body or in the lower extremities are rarely seen. He felt that the only difference between Harada's disease and the Vogt-Koyanagi syndrome was that in the former condition the uveitis was largely confined to the posterior pole and tended to be highly exudative, whereas in the latter the uveitis was more severe and affected the entire uvea equally, with less tendency toward exudation.

Wadsworth[17] stated that the hair and skin changes of the Vogt-Koyanagi-Harada syndrome are rarely seen in cases of sympathetic ophthalmia. However, Fine and Gilligan[18] reported poliosis and vitiligo in two cases of sympathetic ophthalmia after cataract extraction. We have seen a case of sympathetic ophthalmia after cataract extraction in a 40-year-old man who later developed dysacousia, alopecia, poliosis, and vitiligo, with a suggestion of subretinal exudation in the sympathizing eye. It would appear well-established that these accessory symptoms and signs may be found in any of the three entities.

Early in the course of her disease our patient had a transient increase in intraocular pressure, with secondary glaucoma evident three years later. Whether this glaucoma is directly associated with the uveitis or secondary to prolonged steroid therapy, as described by Laval,[19] is difficult to ascertain.

This case appears to be one of unusually severe and prolonged involvement of the uveal tract. Prognosis in Harada's disease is extremely variable. Recovery in one eye is not infrequently seen, with complete loss of vision occurring in the fellow eye. Mitsui's prognosis in our case may have been affected by the improvement in status wrought by the steroid therapy before he had seen her. In general, it would appear that in those cases of Harada's disease in which there is a marked elevation of the retina with bullae, the prognosis is less favorable than in those in which there is only a flat detachment. This patient obviously has a most severe and extensive uveal involvement.

Summary

An 8½-year-old white girl developed classical symptoms and signs of Harada's disease three weeks after an upper respiratory infection.

Associated with cells and flare in the anterior chamber were vitreous opacities and bullous retinal separation.

Cerebrospinal fluid pleocytosis was noted. Later poliosis occurred.

The patient was treated for over three years with oral steroids—primarily prednisone (Meticorten). After three years, signs of activity persist and increase whenever the steroid is withdrawn.

Previous reports of this condition are discussed, and I concur with those who feel that Harada's disease, the Vogt-Koyanagi syndrome, and sympathetic ophthalmia are essentially the same disease—granulomatous uveitis—and that prolonged steroid therapy is sometimes beneficial and is the treatment of choice.

Eye Bank for Sight Restoration, 210 E. 64th St. (21).

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Peculiar Color Blindness in Peculiar People

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Introduction

When a gene for any of the sex-linked "red-green" color blindnesses finds expression in an ordinary male, it is only rarely that the defect it produces is anything but regular, i. e., with characteristics that vary within narrow limits and leave the defect easy to classify. Color blindness in females is subject to more variation, in proportion to the numbers affected at all. Most people who have only casual contacts with color blindness, for example, those who administer vocational screening tests without really understanding them, suppose vaguely that color-blind females are rare and perhaps accidental. They can hardly be blamed for imagining that each such female may have a unique defect.

This is not the situation. But while many, and probably most, color-blind females are in no way "accidental" and have defects identical with those which the same genes would produce in males, the defectiveness of the small color-blind female population *is* more heterogeneous both physiologically and genetically than anyone realized until very recently. There is a discrepancy between the number of color-defective females actually found in almost any population and the theoretical number calculated on any reasonable basis. The persons who account for the discrepancy are all genetically peculiar in one way or another, and it is among these persons that the physiologically peculiar, "no-two-alike," irregular color-blindness systems appear to be concentrated.

The classical surveys of partial color blindness made in large general bisexual populations (Waaler, 1927; von Planta, 1928) showed that about 8% of white European males have one or another of the red-green defects: protanopia, protanomaly (protanomalous trichromasy), deuteranopia, and deuteranomaly (deuteranomalous trichromasy). These and the genes for them are commonly designated by the symbols *P*, *PA*, *D*, and *DA*.

If these were all allelic, the incidence of color blindness in females would be the square of 0.08, or 0.0064, =0.64%. Waaler's and von Planta's studies revealed only 0.43% or 0.44%. Some investigators, even modern genetically sophisticated ones, seem to be content if they can explain this sizable discrepancy. They (e. g., Pickford, 1956, 1958) appeal to Waaler's own two-locus hypothesis, under which the *P* and *PA* and an N_p normality gene are allelic at one X-chromosome locus, with the *D* and *DA* genes (and an N_d) interchangeable at a distinct (although closely adjacent) locus. Since *P/D*, *P/DA*, *PA/D*, and *PA/DA* females should all be color-normal, their subtraction from the "theoretical affecteds" would pull the 0.64% of the latter down to 0.40%, from which the observed 0.44% of actual affecteds does not differ significantly.

This sort of analysis assumes that all color-blind females are *P/P*, *P/PA*, *PA/PA*, *D/D*, *D/DA*, or *DA/DA*. It is, however, inadequate; not that any important number of X-chromosomes contain two defect-genes each, for crossing-over between the protanoid and deuteranoid loci is to all intents and purposes nonexistent, but the numbers of homozygous and allelic-

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Gene in Maternal X-Chromosome	Gene in Paternal X-Chromosome: *P* (in 0.01)	*PA* (in 0.01)	*D* (in 0.01)	*DA* (in 0.05)
P in 0.01	0.0001 show *P*	0.0001 show *PA*	Normal	Normal
P in 0.01	0.0001 show *PA*	0.0001 show *PA*	Normal	Normal
D in 0.01	Normal	Normal	0.0001 show *D*	0.0005 show *DA*
DA in 0.05	Normal	Normal *	0.0005 show *DA*	0.0025 show *DA*

* Mrs. Grant also has this genotype.

compound-heterozygous females could not total to 0.44% of all females in a very large group.

The relative incidences of the different genes in X-chromosomes must agree with the relative incidences of the defects in males. These incidences are known very accurately, for with the figures of Waaler and von Planta there can be lumped the data from many later surveys of purely male populations (François et al., 1957). In round numbers, in every 100 males there are 1 protanope, 1 protanomal (ordinary or extreme), 1 deuteranope, and 5 deuteranomals (ordinary or extreme; Walls, to be published). Assuming strict adherence to the dominance sequences $N_p \rightarrow PA \rightarrow P$ and $N_d \rightarrow DA \rightarrow D$, the incidences of the expected red-green color-blind female phenotypes will be as displayed in a Punnett square (Table).

These total to 0.0040, or 0.40% of all females. This value is indeed far enough away from 0.64% to support the two-locus hypothesis powerfully, but it falls short of the observed 0.44%, although to a statistically insignificant extent. Paradoxically, however, one knows that a real discrepancy, of some value or other and in this direction, *must* exist, for, one knows that there are color-blind females who do not find places in the theoretical square.

Until only four years ago, all such persons would have been assumed to be "manifesting heterozygotes," women with a single one of these generally recessive genes but color-blind nevertheless. Such a woman may be identified through having had a color-normal father or a color-normal son. Even while the sex-linked inheritance of the red-green defects was still being worked out, the literature already exhibited such cases (e. g., Siemens, 1926). At all times there have, of course, been some skeptics who waved the banner of *pater semper incertus*. There are even prominent contemporary investigators (e. g., Pickford, 1958; Lenz, 1957) who appear not to acknowledge the existence of manifesting heterozygotes.

Undoubtedly (see below) they do exist, but at present no one can say how many color-blind females outside of the square are manifesting heterozygotes and how many are something else. This "something else" is an assemblage of persons who ostensibly are females but have only one X-chromosome instead of two, so that they can be color-blind on the basis of a single gene. Some of them may have a Y-chromosome, and any such persons are genetic *males*. They comprise the victims of two particular conditions which, by definition, are pseudohermaphroditisms. They are "intersexes" but not in the lay sense: they are not mannish women or womanish men but appear entirely feminine in street clothes and can stroll through any powder room unsuspected—even by themselves. Unless they have been examined by an expert and unwisely told of their true status, these people consider themselves to be women and have no reason to think otherwise. They seldom have ambiguous genitalia, with any such features as an imperfectly closed scrotum, a miniature vagina, or an uncanalized phallus too small to call a penis and too large to seem a clitoris.

The bearers of these intersexual conditions—now known as gonadal dysgenesis and testicular feminization—would appear to have the same relatively high probability

of being color blind as normal males. Their color-blind representatives, undiagnosed as intersexes in the past, have assuredly loaded somewhat the statistics of "color-blind females." Those who chanced to have color-blind fathers would have raised no doubts of any kind. Being sterile, none of them could have drawn attention by having had a color-normal son, but at least those who happened to have color-normal fathers would have been set down as manifesting heterozygotes by alert investigators.

How many of the color-blind females who have only one color-blindness gene are indeed manifesting heterozygotes and how many have one X-chromosome and no Y("XO") or are genetically male (XY) intersexes passing as females even to their parents and their husbands is a problem that could only now be realized to exist. Fortunately the same new "nuclear sexing" procedure that has uncovered the problem gives us the means of working at its solution. Since no one is likely to survey 100,000 or so run-of-the-mill females for color blindness, we are not likely ever to have an accurate figure for the total discrepancy between theoretical and observed color-blinds. The most that we can hope for is a fairly accurate determination of the relative numbers of the two classes of "nontheoreticals."

To be strictly accurate to a satisfactory number of decimal places, we should even begin to be cautious in evaluations of the percentage of color-blind men—for the numbers of color-*normal* males are, we have lately learned, falsified by the inclusion of ostensible men who have two X-chromosomes with or without a Y, the victims of still another not uncommon "intersexual" state: "true" Klinefelter's syndrome. These may comprise 0.1% of all "males" (Prader et al., 1958).

Color Blindness and Intersexes

The Possibilities.—Connections of one kind or another between color blindness and pseudohermaphroditism have been suspected and suggested for many years. Some have finally been found (or thought to have been) and are now being explored and exploited with increasing velocity.

The most direct of these connections is the one postulated by Kallmann, Schonfeld, and Barrera (1944). They were led to believe that in a whole class of intersexes, eunuchoid in habitus and genitalia, the primary hypogonadal condition is in a sense caused by color blindness—that is, a hypothetical X-chromosomal aberration which caused color blindness was also the cause of the eunuchoidism through a disturbing effect upon the sex-determination mechanism. This theory will require thorough examination, but even if it is then discarded, it has to be credited with having alerted endocrinologists—some of them at any rate, who have carefully checked for color blindness *every* intersex who has gone through their hands since.

As early as 1931, Goldschmidt suggested that in the case of any type of intersex, however ambiguous anatomically, the true "gametic sex" (i. e., the sex chromosome pattern—XX or XY.) might be ascertained by looking at the incidence in the group of any common sex-linked trait. (Goldschmidt's own well-known theory of sex determination required *him* to assume that any and every human intersex would have two X-chromosomes.)

Eventually this suggestion was followed at least once, by Sørensen (1953), who attacked the problem of the "true" (genetic) sex of persons with hypospadias. Sørensen accumulated 104 cases, among whom 7 were found to have red-green color blindness of one kind or another. This showed clearly enough that hypospadiacs have XY-chromosomes, for 8.32 out of 104 would then be expected to be color-blind. Among 79 of the fathers of Sørensen's hypospadiacs, 9 were color-blind (but could not have passed *their* defects to XY progeny). Of 83 mothers available for examination, none was color-blind, but of course there would have been about 16 heterozygous "carriers" among 104 mothers.

Sørensen did his work just too soon to be able to take advantage of the findings

of Moore, Graham, and Barr (1953), who were the first to show that the apparent sex-chromosome pattern of an intersex (or of anyone) can be deduced from the presence or absence of a particular small mass of chromatin in intermitotic somatic nuclei.

Such "nuclear sexing" can be done on smears of buccal scrapings or of blood or on a squash or section biopsy of almost any tissue—skin being preferred (Jones and Scott, 1958; Grumbach and Barr, 1958, for latest techniques). One looks for a special small mass of chromatin adherent to the nuclear membrane. This is generally believed to represent the conjoined heterochromatin portions of two X-chromosomes. If seen in 40%-90% of the cells, it signifies that the tissue came from a presumptive genetic female—the donor then being said to be "chromatin positive." The mass is probably present in nearly all if not all cells in the sample and invisible in some only because of unfavorable orientation. In a genetic male (XY) or in an XO human, there is not enough X heterochromatin to form a detectible mass in more than a few of the cells and the donor is called "chromatin negative."

With blood smears, the criteria are very different. In a sample from a female donor, a tiny mass connected by a thread to a lobe of the nucleus can be found in 2% or 3% of the mature neutrophils. This complex, resembling a bass-drumstick, was believed for several years to be the leukocyte's special version of the 2X heterochromatin "chromocenter" of tissue cells. Decision between chromatin-positiveness and chromatin-negativeness required the examination of at least 500 neutrophils, but chromosomal sexing on blood was nevertheless considered perfectly reliable, although tedious. Lately, however, so many reports have accumulated of discrepancies between the genetic sex indicated by "drumsticks" and that indicated by tissue nuclei (Ashley and Jones, 1958) that blood can no longer be considered fully reliable. The drumstick ball, while somehow genetically determined in relation to sex, is itself *not* the X heterochromatin, for it and the usual sex-chromatin mass may be seen in the same cell. A buccal-mucosa smear remains the simplest material on which reliable nuclear sexing can be done.

This is a little sad, for the nonmedical investigator cannot secure a mouth scraping from an ambiguous color-blind female as easily as he can obtain a drop of blood from her pricked finger. It is psychologically essential to keep the subject from knowing that she is even suspected of having perhaps the sex chromosomes of a male. The purposes of a blood smear are known to be many and various, and it is not hard to give a plausible reason for wanting to make one. But a woman solicited for a mouth scraping may know that it could only be wanted—by a nonmedical man—for a determination of basic sex, or, if she goes away and asks her medically sophisticated friends what it might have been needed for, one of them may be foolish enough to tell her.

The "chromatin-negative" nuclear characteristic does not mean for sure that a Y-chromosome is present but only that two entire X-chromosomes are not present. In one or another of the intersexual conditions upon which so much attention is currently concentrated, it is perfectly conceivable that such sex-chromosome combinations as "XO," "X+½X," "XXY," etc., may be the rule. There are investigators in this field who think they have already indirectly identified persons with one X and no Y (Lenz, 1957; Gray, 1958). Very direct identifications (in metaphases) of XO and XXY conditions have lately been made (Ford and Polani, 1959). Nuclear sexing, as done at present, would not distinguish between XO and XY situations nor between XX and XXY situations.

It cannot, then, be assumed here that all persons with chromatin-positive nuclei are XX persons (chromosomal females, genetic females) and that chromatin-negative persons are always XY-chromosomal or genetic males. The implications for the association of a high incidence (*ca.* 8%) of color blindness with a single X-chromosome and of a low incidence (*ca.* 0.4%) of color

blindness with two X-chromosomes are the same whether a Y-chromosome is assumed to be present or not. We shall have to use "chromatin-positive" to cover both XX and XXY persons and "chromatin-negative" to include XY and XO persons.

With the advent of nuclear sexing, endocrinologists have been prompt to invoke color-blindness incidences to confirm the sex-chromatin situations found in persons with imperfect sexual anatomy. The pioneering study here was that of Polani, Lessof, and Bishop (1956) on gonadal dysgenesis. Such studies have, however, led to seemingly conflicting results on Klinefelter's syndrome—helping to multiply the cytogenetic hypotheses of the etiology of this condition (see below).

Color-blindness checking has so far been unfruitful in respect of testicular feminization. This is especially a pity—not that an 8% incidence of color blindness is essential to confirm the "one X±Y" condition in this startling syndrome but because more than one investigator has pointed out how only color-blindness families containing testicular feminization will ever show the mode of inheritance of that syndrome. At present, it is impossible to decide between autosomal dominance and X-linked recessiveness, and there are reasons why one investigator will find it difficult to pile up statistically significant data on this syndrome or to find other data with which his own can be pooled (see below).

Finally, the endocrinologist can of course turn around and assist the color-blindness investigator by helping him to distinguish manifesting heterozygotes from color-blind "females" who are actually hemizygotes. By referring the latter to the color scientist for really thorough testing, he may speed the day when we will know for sure whether a single color-blindness gene in a phenotypically female body always, or often, or only sometimes has an unusual action if it has any large effect at all, and produces an irregular version of the defect it would call for in the environment of a male body.

Kallmann's Theory.—This theory may seem to take up a disproportionate amount of space here, but in my opinion it is extremely important that this ghost be thoroughly laid. If those who may read the theory do not also appreciate how destructively it can be criticized, there is danger that the more the incidence of color blindness is used and discussed in connection with intersexes, the more endocrinologists will say, "But those figures probably mean nothing—look at the relationship Kallmann established."

Kallmann, Schonfeld, and Barrera (1944) reported on three pedigrees of primary hypogonadal (hypogonadotropic?) eunuchoidism in which there were so many color-blind persons—including most of the eunuchoids, one of them female—that they were led to postulate that the color blindness was in a sense the cause of the eunuchoidism. Every eunuchoid in all three families had a color-blind ascendant. Closely associated also with the eunuchoidism were complete anosmia and synkinesia. Mental deficiency was less widespread among the eunuchoids. The three families offered, all told, 12 eunuchoids, of whom 8 were color-blind; 9, anosmic; 5, synkinetic, and 2, mentally defective. Fourteen noneunuchoid members of the families were color-blind, and three of these were mentally deficient. The authors considered "extravagant" the idea that color blindness should have been so common in the three parts of Russia from which the families hailed as to account for their large numbers of color-blind members. They were sure that they were dealing with a special situation.

The kind(s) of color blindness involved cannot be determined. The tests applied were the Holmgren, Stilling, and Ishihara —none of them of much value for differential diagnosis. On this basis, various persons were deemed totally color blind, almost completely color blind, completely red-green blind and partially blue-yellow blind, severely red-green blind, etc. The pedigrees are not, however, in the least inconsistent with

the assumption that throughout each family some single kind of severe defect (dichromasy) was involved. Unless an anomaloscope is used, a protanope or deuteranope —even if not mentally deficient—may easily be supposed to be totally color-blind or nearly so. Every layman knows of a "totally color-blind man" in his neighborhood who is really only a dichromate.

No unbelievably high incidence of color-blindness in the Russian home areas need be contemplated. The chance occurrence in two of the families of homozygous color-blind females and the marriage of one of these to a color-blind man sufficiently explains their high percentage of color-blind members. Kallmann et al., however, offered a truly extravagant hypothesis: The color blindness in these families, whether physiologically special or not, had a special genetic basis. It was due to a special mutation but not a gene mutation. Rather, breakage and perhaps translocation in an X-chromosome constituted the color-blindness mutation in itself or was responsible for it by way of a position effect. This chromosomal aberration, by upsetting a Goldschmidtian mechanism of sex-determination, was also responsible for the eunuchoidism (and, along another route, for the other associated defects).

Kallmann et al. implied criticism of other investigations of familial eunuchoidism, because the reports failed to mention either the presence or absence of color blindness. They suggested that many a color-blindness family under genetic investigation contains eunuchoid color-blinds who conceal their hypogonadic status from the investigator. They did not go so far as to say that all color-blinds should be checked for eunuchoidism, but they did plead for determinations of the incidence of color blindness in eunuchoids. They would concede that the association of color deficiencies with gonadal anomalies might be coincidental, only if "further studies supply a series of eunuchoid sibships without color blindness or any other sex-linked anomaly in their ancestry." Just such purely eunuchoid sibships—three brothers, and a brother and sister—have been described by Biben and Gordan (1955), but no amount of such evidence is needed to demolish the hypothesis of Kallmann et al.

In Family "A" there was no color-blind female. The three eunuchoids (all color-normal) and the four color-blind males were so distributed that the X-chromosomes containing the color blindness gene clearly did not contain an eunuchoidism gene, whereas other X-chromosomes could have contained such a gene—making the eunuchoidism a simple X-linked recessive character like the color blindness itself but associated with the latter purely fortuitously in this family. On the other hand, the anosmia and the eunuchoidism appear here to have been carried in the same X-chromosomes, if not indeed caused by the same (pleiotropic) gene.

Since color blindness and eunuchoidism were not combined in any "A" person, Kallmann et al. had to go to special lengths to claim a causal connection there. They had to assume either that (*a*) the two eunuchoid sons of a color-blind father were really female hermaphrodites, heterozygous for color blindness and therefore not showing it, or else that (*b*) these two eunuchoids were either genetic females (XX) homozygous for color blindness or else genetic males with the color-blindness gene (from an assumedly heterozygous mother) and with the color-blindness gene(s) not manifested in either event in consequence, somehow, of already having caused eunuchoidism, anosmia, etc.

In Family "B" there was a homozygous color-blind matriarch. She had one fertile and four anosmic eunuchoid sons, all color-blind (as they would have to be), and one color-normal daughter. This daughter married a color-blind man, while her fertile brother married the latter's cousin, who showed herself to be a color-blindness carrier by producing color-blind monozygotic twin sons (and two color-normal daughters). Meanwhile the married sister of the four eunuchoids was generating two

anosmic, color-blind, eunuchoid sons, proving herself to be heterozygous for all three defects. Everything about Family "B" fits the simple idea that the color-blind matriarch had a color-blindness gene in one X-chromosome (which she gave to one son), and a non-normal allele of it and a gene or genes for eunuchoidism-and-anosmia in the other X (which she passed to her other children). There is no reason to think that the color-blindness gene borne by the consanguine man and women who married into the family was even at the same locus as that of the color-blindness gene in the eunuchoids.

In Family "C" a color-blind man was married twice. One wife may have carried color blindness, for by her he had five daughters, one of whom died in Russia and was mentally defective and *reputedly* color blind. The other wife was herself color-blind, and by her he had three children, all eunuchoid. One of these stayed in Russia (and should have had to be color-blind, although his American relatives supposed that he could not be since he was a successful silk merchant!). A second of these eunuchoids was also male and was color-blind but not anosmic. The third was the only person in Family "C" who keeps it from being readily interpreted exactly like Families "A" and "B." For this eunuchoid was a female, color-blind, anosmic, deaf, diabetic, and mentally deficient. One wonders how she could be eunuchoid if her mother could give her only one X-linked recessive gene for that condition and why her American eunuchoid brother was not found to be anosmic. It seems most likely that in this particular family the eunuchoidism gene was X-linked and nominally recessive and that in the American male eunuchoid it had a mild action (not producing anosmia), while in his sister it had a multiple and disastrous action even though she was only heterozygous for it. In the "C" Family, however, just as in "A" and "B," the inheritance of the color blindness was entirely orthodox and was exactly what it might have been in any noneunuchoidism family. There is not the slightest reason to suppose that it was based upon a chromosomal aberration, a position effect, or anything but a genic allele or alleles at either the protanoid or the deuteranoid locus.

Kallmann was sure that not only the hypogonadism and the color blindness, but anosmia and mental deficiency, were pleiotropic expressions of a single chromosomal aberration in these three families. Several studies he was able to cite showed an association of anosmia with eunuchoidism, and indeed the only pedigree he could find of anosmia standing alone was that of Glaser (1918), in which X-linked recessive inheritance was suggested, though not proved. In the anosmia literature compiled recently by Canciullo (1957), however, no relationship to the determination of the genitalia appears, and the original pedigree contributed by Canciullo exhibits hologynic inheritance of the anosmia.

Kallmann called for studies of the incidence of sexual maldevelopment in the offspring of color-blind parents, and for studies of the incidence of color blindness not only in "all eunuchoids" but in "certain groups of mental defectives." These latter were not particularized but alluded to in other paragraphs only by the terms "mental deficiency" and "mental defect." Apparently, what were contemplated were the mental features of the Laurence-Moon-Bardet-Biedl syndrome and Froelich's syndrome. In the early history of color blindness it was common to suppose a relation to mental deficiency, and color blindness was sometimes considered a mental (perceptual) defect in itself. From the most recent studies of the "relation," the situation appears to be a standoff: O'Connor (1957) found a nearly twice-normal incidence of red-green color blindness in male imbeciles and a normal incidence in feeblemindeds (morons), but Kratter (1957) found a normal incidence in imbeciles and a half-normal incidence in morons. Neither author referred to the paper of Kallmann et al., although all three papers appeared in the

same journal. One's impression that mentally abnormal persons are simply unreliable color-blindness testees is only heightened by reading the claim of Kaplan and Lynch (1945), that (e. g.) 33% of male schizophrenics are color-defective.

Gonadal Dysgenesis.—General: In gonadal dysgenesis the gonads are abdominal and almost never contain any cells in any stage of gametogenesis. Their tissue was formerly mistakenly identified as ovarian stroma. The gonads being thought to be ovaries (streak ovaries), the condition was for a time called "ovarian agenesis." Actually, the gonads do not progress in organization beyond those of an embryo less than 50 days old, and in the adult they are still neither ovaries nor testes. The person's entire reproductive system remains juvenile but is feminine by default just as is that of a rabbit of either potential sex castrated at any time up to the threshold of the fetal period. The simple rule is that the internal and external genitalia develop "female" unless differentiated testes secrete hormones which make them develop "male."

The first feature noticed to be associated with the primary amenorrhea (betraying the "aplastic ovaries") and the undersized genitalia was short stature. Then in a group of seven such young women who also happened to have pterygium colli (present in one-third of cases) and cubitus valgus (less common), H. H. Turner (1938) discerned a syndrome which was named for him some years later. Meanwhile the very high FSH titer which characterizes the condition (implying the *absence* of ovaries) was noticed. Three studies in 1954 independently revealed that in most cases the somatic nuclei are negative with regard to sex chromatin. Finally, the first chromatin-negative cases to be studied as regards somatic mitotic metaphases have proved to have only one X-chromosome and no Y (Ford and Polani, 1959). Such persons are *not* "genetic males"; in only one chromatin-negative Turner have follicles and ova been seen (Greenblatt, 1958).

Many bodily defects, mostly minor, have sporadic distribution among the victims of gonadal dysgenesis (Lenz, 1957; Jones and Scott, 1958). What little evidence there is for its inheritability seems to tie gonadal dysgenesis to Status Bonnevie-Ullrich (Lenz, 1957; Hoffenberg and Jackson, 1957), which would mean that it is based upon a pleiotropic gene. The most nearly normal-looking persons (with average height, etc.) are most likely to be ones who are chromatin-positive and presumably have two X-chromosomes (Lenz, 1957). Such persons, having no germ plasm, are not sexually normal, but they are not intersexes and, even if they are not identified, they should not cause confusion in the interpretation of color-blindness pedigrees. Neither should the rare case of "Turner's syndrome in a male," whose external genitalia are eunuchoid.

In some small series of cases the number found to be chromatin-negative has been as high as 6 out of 7 or 20 out of 22 or as low as 8 out of 18. Larger compilations indicate 80% or more (Lenz: 156 out of 195; Segal and Nelson, 1957; 98 out of 117). Grumbach and Barr (1958) find over 88% (90 out of 102) of Turners to be chromatin-negative. Under the "embryonic castration" hypothesis, it would seem that if 85 Turners out of 100 are XO, 50 may have started out as XY zygotes, losing the Y in an early cleavage, the other 35 having similarly lost one X. More likely, nondisjunction of X and Y creates O sperms which then fertilize X eggs. The XO condition may bring on the "castration," but why the 15 XX Turners out of 100 are subject to this effect remains a mystery.

Fortunately, the majority of cases of gonadal dysgenesis are likely to be easy to spot in their street clothes. The nonmedical color-vision researcher or geneticist will be alerted by any teen-aged or adult woman not quite 5 ft. tall with a childish voice, with or without a webbed neck or bent elbows. He can ascertain whether there is primary amenorrhea by burying among "health" questions of various kinds a casual

query about the regularity of cycles, etc. He cannot secure a skin sample or a vaginal smear, and he may be hard put to explain why he wanted to scrape oral mucosa, but he is advised to try—or else to solicit the cooperation of the woman's physician, who may or may not already know that she is a "Turner's."

Prior to puberty, the gonadal-dysgenesis girl may suggest her status by exhibiting small stature and a history of low birth weight. It should not be deemed too much trouble to obtain a sex-chromatin determination from *any* color-blind young girl, however—"just in case." Even if the father is color blind (and even in the same way), the child may have only a *maternal* X-chromosome, containing a color-blindness gene, with no normality gene to dominate it.

The first report of color blindness in this syndrome was that of Polani, Lessof, and Bishop (1956), who looked for color blindness in 25 cases as a means of confirming the significance of nuclear-sex determinations. Here, foreknowledge of a presumptive XY situation in 20 of them led the workers to expect a couple of color-blinds. They found four. None of their other (XX) cases was color-blind.

Lenz (1957) was able to add an unpublished "red-green weak" case of Turner's syndrome reported by letter to him by Wilkins, in 1956, and described a case of his own. This was of a 15-year-old girl with gonadal dysgenesis and negative for sex chromatin, who was diagnosed as deuteranopic with the Nagel anomaloscope. Both parents were color-normal, but two maternal uncles had been rejected for the Luftwaffe and had always confused greens and browns and the girl's little brother was "markedly red-green weak" on a wool (Holmgren?) test but too young for any sharper diagnosis.

R. G. Frey, a Viennese ophthalmologist, has lately told me by letter of a deuteranopic girl, whose father is also deuteranopic and whose mother and brother are color-normal. She might have been homozygous (with a heterozygous mother), or she might have been a manifesting heterozygote (with a homozygous-normal mother), but the girl presented features which suggested gonadal dysgenesis. Frey secured a sex-chromatin determination, which was negative, showing that the girl must owe her one deuteranopia gene to a heterozygous mother.

It is too early, of course, for any confirmation of expectation as regards the relative incidences of protanopia, protanomaly, deuteranopia, and deuteranomaly in chromatin-negative females with gonadal dysgenesis. The proportions should be the same here as in sexually perfect males—1:1:1:5.

Gonadal Dysgenesis.—Report of a Case: In 1952, I was told of a 19-year-old girl, color-blind but with color-normal parents, and investigated the family. The girl, Case 1, was essentially deuteranopic. Her parents were indeed color-normal, as were her younger sister and still-younger brother. Her mother's father, reputed color-blind, proved to be a typical deuteranope. It seemed clear that Case 1 was a manifesting heterozygote for deuteranopia and eventually she was so described in print (Walls, 1955).

The "deuteranopia" of Case 1 was irregular, that is, it had features which made it differ from deuteranopia as seen in males and in homozygous females. She saw only two hues in the spectrum and had the expected relative luminosity curve, and her anomaloscope settings were deuteranopic, but her RDP-report and neutral point were unique. Instead of seeing no RDP at all (Walls and Mathews, 1952), she saw a Type I pattern and, moreover, said that its purple had "a lot of red in it." (What sensation she may *call* "red," one does not know, but the point is, deuteranopes do not *say* they see a reddish RDP.) The neutral point of Case 1 with respect to C. I. E. Source C as a standard white light (6,700 degrees K) lay at λ494.2 mμ. The neutral points of 19 protanopes as determined with the same apparatus ranged from 488.5 to 493.6 mμ, those of 14 deuteranopes from 495.2 to 501.8 mμ. The value of Case 1 was thus in an intergroup no man's land, the realness

of which has since been abundantly confirmed (Walls and Heath, 1956).

Everything about Case 1's color defect was consistent with the idea that its basis lay in abnormal circuitry in the pathways above the retina or, at least, above the receptors. In this respect she aligned with an indubitable manifesting heterozygote for protanopia, Case 2, and with other cases in the literature (Walls, 1955). She thus contributed to a hypothesis that when a single color-blindness gene does have a marked action in a female, the defect it produces is irregular—it is not just the one which the same gene would produce in a male—and the action appears to hit only the pathways and to spare the receptors.

There were things about Case 1, also, which suggested prenatal cerebral damage (chemotic in her case) as a possible cause of the manifestation of her one deuteranopia gene. Here, too, she aligned with at least some manifesting heterozygotes, Case 2 and the Dionne quintuplets, for example. Her mother was only 18 when Case 1 was born. She was carried a full month past term, was born only then by courtesy of castor oil and quinine, yet weighed only 4 lb., and was managed about like a premature. She grew up to be short and plump, retained a childish voice, and had not yet menstruated at 18, when exogenous hormone therapy was instituted in keeping with a childhood diagnosis of "hypopituitarism."

Becoming aware of the possibility that Case 1 was a chromosomal male, I regained contact with her for additional visual testing and on a pretext made some blood smears. These were read by Dr. Melvin B. Black, whose pronouncement was "undoubtedly male" (i. e., chromatin-negative). Now 26, Case 1 has been married two years. She is 59 in. tall, weighs 168 lb. Her neck is thick but not webbed; her elbows are practically straight. She knows of no defects other than her primary amenorrhea. She certainly has gonadal dysgenesis. I found that her present general practitioner, to whom she has gone primarily for a weight-reduction program, had not made that diagnosis and in fact had never heard of Turner's syndrome.

These facts about Case 1 are set forth in such detail for two purposes: to show how easily a color-blindness investigator may be led to think he is dealing with a manifesting heterozygote when he is not and to make it clear that the irregularity of the "deuteranopia" in Case 1 was noticed and interpreted as suprareceptoral before she was discovered to have only one X-chromosome. The irregularity can now be further annotated. Recently Case 1 was given the AO H-R-R test (under 6,700 degrees K light). She read all of the "blue-yellow" plates without error but saw *no* characters on the "red-green" plates with the exception of the "O" on the last plate (No. 16). Applying the scoring rules rigidly, this would make the color blindness of Case 1 a "strong protan" defect! It would be more reasonable to relax the rules enough to call it a "strong red-green defect, unclassified as to type." In any event, her performance was unique. For her to read neither deutan nor protan characters is, however, entirely to be expected, if her 6,700 degrees K neutral point is between the ranges of protanopic and deuteranopic neutral-point wave lengths and the AO H-R-R characters have the dominant wave lengths they were intended to have (Walls, to be published).

On the same occasion (1958), the neutral point of Case 1 was redetermined with respect to N. B. S. Source D (7,500 degrees K). Curiously, the difference of whites did not move the empirical neutral point violetward; it was found to be at λ494.1 mμ. The result of this was that with respect to 7,500 degrees K white, the neutral point of Case 1 is barely *not* in the intergroup no man's land. At this writing, my data contain 25 protanopic 7,500 degree K neutral points ranging from 488.7 to 492.0 and 25 deuteranopic values running from 493.2 to 503.8 mμ. Only one of these latter is at a wave length shorter than that of Case 1.

Testicular Feminization.—In testicular feminization ("Goldberg-Maxwell syn-

drome") the person's sex of rearing and social sex are invariably female. As an adult in street clothes, her invariable status as a sex-chromatin-negative (and probably an XY "chromosomal male") is perfectly concealed. Her eunuchoid proportions (high ratio of span to height) are unlikely to attract notice. Her friends may consider her to have a leggy figure—but hardly a boyish one: she seems "all woman" and is likely to be particularly full-breasted. The only sign of her syndrome that may show is a complete lack of axillary hair, but this will not betray her since so many women keep their axillary hair removed.

The testicularly feminized person's reproductive system ordinarily appears unambiguously female, although not quite complete. There is always a vagina which is useful or can be made so, but there is rarely any development of the uterus. The testes are usually abdominal, usually located like ovaries, and even look like ovaries, grossly. They may, however, be inguinal or even embedded in the labia majora. In such locations their painfulness when pressed instigates their surgical removal.

These women are as likely as any to marry, and happily unless they very much want the children they cannot have. Uterus or no, primary amenorrhea is inevitable, and the testes produce no functional gametes of any kind.

The investigator of an ambigously color-blind, normal-looking female can identify her as an instance of testicular feminization if she admits to the lack of menstruation and axillary hair (she will then lack pubic hair also, but this will not have to be disclosed). The finding of "chromosomal maleness" via a buccal smear will be clinching. The patient must not then be told of her genetic status, but she may know of it already and evade questions or procedures which would confirm it. There have been at least 90 cases reported, for this number of *familial* ones, known to him, is mentioned by Lenz (1957). Undoubtedly hundreds are identified without report (Gordan, personal communication). The average patient being perfectly marriageable and completely disguised even from the average husband, the obvious dangers of gossip and blackmail keep her gynecologist from publishing on her by masked photograph or even by initials. Testicular feminization may be "the most arresting syndrome in intersexuality" (Jones and Scott, 1958), but it is the one which the medical student is least likely to be shown in the flesh.

This syndrome is certainly hereditary, and one may speak of a carrier state, since mothers and aunts of affected daughters may also lack axillary and pubic hair. In lumped sibships, the number of affecteds exceeds the number of normal males but the sum of the two groups equals the number of normal females (Grumbach and Barr, 1958). Unless and until chromosomal counts on metaphases indicate otherwise, it can be assumed that a Y-chromosome is present, although with its masculinizing power somehow reduced or counteracted.

Lenz (1957) pleads for a sharp watch for color blindness in the families of affecteds, since without marking of X-chromosomes by some relatively common X-linked gene, it cannot be firmly decided whether testicular feminization is inherited as a sex-linked recessive or as a sex-limited autosomal dominant (which, as a minimal expression, apparently suppresses the follicles of sexual hair). Independently, Grumbach and Barr (1958) have pointed this out also. Lenz could learn of only two cases found to be color-blind up to 1957, one of them ("red-green weak") reported by letter to him by Wiedemann in 1956, the other ("red-green blind") a little later by Napp.

Klinefelter's Syndrome.—In a characteristic case of this syndrome the person is "all man" in habitus and genitalia but is chromatin-positive—the antithesis of the victim of testicular feminization. The only invariable clinical sign is an undersized condition of the testicles, which are rarely larger than $1.5 \times 1.0 \times 0.5$ cm. For this reason Ferguson-Smith (1958) prefers to call the syndrome primary microrchidism rather

than by any of its many other suggested names which describe no overt stigmata.

Under the original eponym, at least two conditions are included. An early distinction was made between "typical" or "true" Klinefelter's and "false" Klinefelter's syndrome (Klinefelter, 1958). In the former the seminiferous tubules were very dysgenetic, either fibrotic or hyalinized, and very rarely produced any spermatozoa. In the latter their somatic tissue was more nearly normal and the germ tissue more abundant, although spermatogenesis all the way to spermatozoa was supposed to be unusual. Upon the advent of nuclear sexing, it was soon believed that the "true" cases were all chromatin-positive, the "false" ones chromatin-negative. The occasional chromatin-positive case whose ejaculate contains motile sperms was believed to represent complete sex-reversal, with a counterpart in the very rare case of Turner's syndrome who forms ova but is chromatin-negative (Greenblatt, 1958). Actually neither a fertile Turner nor a fertile Klinefelter could be considered sex-reversed at all, if the Turner is XO and the Klinefelter is XXY (see below).

The sharpness of the difference in tubule histology (basing the "true" versus "false" distinction) in the chromatin-positive and chromatin-negative cases has broken down (Grumbach and Barr, 1958; Ferguson-Smith, 1958). It now seems logical to give more emphasis to the sex chromatin than to the tubular status and to speak therefore of "chromatin-positive and chromatin-negative Klinefelter's syndrome (or primary microrchidism)." This point of view tends to keep attention properly upon the basic genetical puzzle—the occurrence of two chromosomal versions—rather than upon differences which must have a secondary (hormonal) substrate.

Nevertheless the chromatin-positive cases are more likely or very much more likely to have some combination of the most dystrophic tubules (hence the smallest testicles), complete aspermia, supernormal urinary gonadotropins, decreased urinary 17-ketosteroids, eunuchoid proportions, and gynecomastia.

The consensus has been that about 80% of all primary-microrchic males are chromatin-positive. Stewart et al. (1958) believe, on the other hand, that the chromatin-negative and chromatin-positive versions are equally numerous and that each occurs in at least 1 in every 10,000 ostensible males. Prader et al. (1958) raise this estimate to 1 in 1,000, for the chromatin-positive condition at least (which they find in more than 2% of oligophrenic boys).

It is in respect to Klinefelter's syndrome, rather than in either of the one-X conditions dealt with above, that we have the most interesting involvements with color blindness. Here, what to expect as regards color-blindness incidences may seem to depend directly upon the nuclear-sex findings, as indicating the presence of only one X-chromosome or two. But the incidences so far reported have seemed to call into question the very significance of the sex-chromatin findings *in this syndrome* and have added to the hypotheses of its cytogenetic etiology—numerous enough and contradictory enough without such addition.

In the first extensive survey for color blindness in Klinefelter's syndrome, Nowakowski, Lenz and Parada (1958) found a surprising situation. From among 258 males having various degrees of testicular hypoplasia, they were able to select out 37 who were chromatin-positive and had high urinary gonadotropin levels. These 37 were accepted as cases of true Klinefelter's syndrome, irrespective of other symptoms shown or not shown. Of the 37, 3 (8% !) were "red-green weak" (Ishihara) but all three had color-normal fathers. Two of them, however, each had a color-blind brother, and one of the three had a deuteranomalous mother.

The investigators might have concluded that they were dealing with three manifesting heterozygotes. Out of any 37 XX or XXY humans, about 6 would be expected to be red-green color-blindness heterozygotes anyway. For half of these to manifest their

gene would of course be most improbable—unless perhaps the biochemical environment provided by a Klinefelter's-syndrome body somehow encourages such manifestation.

Nowakowski et al. did not even entertain this possibility. They considered that Klinefelter persons, if they have a male-like incidence of color blindness, are not genetically female in the usual sense even if they are chromatin-positive. If they have no Y-chromosome, they are not genetically male either, so they are "chromosomal intersexes." To the minds of these authors the most plausible hypothesis was that an X-chromosome had become broken, with the portion containing the color-blindness loci lost entirely. Such an X, getting into a zygote along with a normal X, determines Klinefelter's syndrome (as a greatly weakened femininity) and allows the person to be color-blind if the normal X happens to contain a color-blindness gene. At the same time, the sex-chromatin mass formed in intermitotic nuclei by the "1½" X-chromosomes in the same, and the same in size, as in normal XX-females, making these nuclei chromatin-positive. There is no conflict here, for "die Teile des x-Chromosoms, welche für die Differenzierung der Gonaden verantwortlich sind, sind offenbar andere als die, welche den Chromatinbefund bestimmen."

There are important immediate objections to this broken-X hypothesis. It does not account for the chromatin-negative "Klinefelters," which may not seem so bad if these comprise only 20% but is serious if they constitute 50% of all, as Stewart believes. If a chromatin-negative person had to have ½ X + a Y, he would surely not be viable. The chromatin-positive would have to have such a chromatin-negative and a fertile one, or else a fertile chromatin-positive, for one parent—or else every Klinefelter would have to represent a separate mutation and more than one case in the same family would be highly unlikely. Occurrence in two generations has indeed been reported only once, but many affected sibships are on record and even some containing both chromatin-positive and chromatin-negative persons (Stewart et al., 1958).

Several other etiological hypotheses have been offered and are discussed or cited by Grumbach and Barr (1958), Gray (1958), and Stewart et al. (1958). Stewart's own is the most interesting, if only because it accounts plausibly for both the chromatin-positive and chromatin-negative conditions with an essentially common mechanism. Moreover, Stewart and his associates have tested "Klinefelters" for color blindness even more extensively than Nowakowski et al. and, while their findings do not support *any* etiological hypothesis involving chromosomal aberrations, they definitely conflict with the color-blindness findings of Nowakowski and thereby weaken, if they do not destroy, the "broken-X" theory.

The first announcement in this connection (by Stewart et al., 1958) was that 16 "K−" and 11 "K+" cases had been seen, that the color vision of most of these had been checked, and that color blindness had been found only among the chromatin-*negatives*. At the time, Stewart did not know of Nowakowski's work. An account of the details of the distribution of color blindness among Stewart's early patients (unfortunately, inaccurate) was published by Pickford (1958); no attention should be given to this. Meanwhile, Stewart continued to accumulate both K+ and K− cases in Glasgow, testing all for color blindness, and arranged with Polani in London and Prader in Zurich to pool their data to build up statistical significance. This goal attained, a joint paper was prepared (Polani et al., 1958) tabulating the data upon 47 patients seen in Glasgow, 35 in London, and 11 in Zurich.

Among 55 K+ none was color-blind, but less than 1 such person (0.22) would have been expected if K+ persons are XX or XXY (4.4 if they are XY). Among 38 K−, 4 were color-blind, as compared with an expectation of 3.04 if K− means XY and 0.15 if it should mean XX or XXY. To the 17 Glasgow K− cases (3 of them color-blind) and the 30 Glasgow K+ cases, Stewart has since been able to add 10 more

K+, all color-normal (personal communication). At least 65 color-normal K+ (and 4 color-blind K− out of 38) can thus be ranged against Nowakowski's 37 K+ containing three color-blinds (combined with no data at all regarding K−).

If these 65 are added to Nowakowski's 37, we have 102 K+. If the 102 have two whole X-chromosomes, about 16 of them should be simple heterozygotes. Nowakowski's three color-blinds, if they are manifesting heterozygotes, constitute 19% of all of the heterozygotes. This may seem fantastic, and yet the conclusion seems inescapable that a highly improbable coincidence has deceived Nowakowski et al. and led them down the garden path of cytogenetic theorization.

The latest information, from actual metaphasal counts, puts the hereditary chromatin-positive Klinefelter on a cytogenetic basis of habitual nondisjunction. So far, five K+ in succession have proved to be XXY (from an X egg and XY sperm or else from an XX egg and a Y sperm); the only K− examined proved to be XY (Ford and Polani, 1959).

The principal problem here for the color-blindness investigator is one of identification. A color-normal son of a color-blind woman can cause her to be falsely labeled a manifesting heterozygote, if the "son" happens to be a chromatin-positive Klinefelter's. Prepubertally, the only sign is undersized testicles, likely to be ignored even by the boy himself. Beyond puberty, gynecomastia commonly appears but may be treated empirically by scarless subcutaneous mastectomy. By manhood, the patient may even have forgotten this operation and may never have known its significance anyway.

If the adult K+ marries, he may or may not discover that either he or his wife must be sterile. He may or may not assume that he is the infertile one. He may or may not present himself to a physician or attend a sterility clinic. Lastly, he may or may not be correctly diagnosed.

So very many of these persons necessarily go unrecognized that what the conscientious color-blindness investigator must do seems clear. Color-blind women with a color-normal son are not numerous. It is not too much trouble to check a buccal smear from *every* such boy to exclude the possibility of his being a chromatin-positive Klinefelter. This check, in itself, may not establish whether the mother is homozygous or heterozygous, but it may enable a diagnosis of the son which otherwise might never be made.

Sooner or later also, a color-blind K+ will turn up whose father shows the same defect and whose mother is color-normal. She will be adjudged a simple heterozygote, and the investigator who has not diagnosed the K+ will congratulate himself upon avoiding the assumption of holandric transmission such as does occur in the unique Cambier family (Reed et al., 1951). Yet father-to-son transmission could be said to have occurred—certainly, if the father and son exhibit an anomalous trichromasy and the mother is heterozygous for the allelic dichromasy. In such a case, also, one could be sure that the XXY-condition arose from an X egg and an XY sperm.*

Manifesting Heterozygotes

Identification and Study.—Excluding XO and XXY persons and XY pseudofemales and assuming that a defect any ordinary XX female shows is exactly the defect which the same gene would produce in an XY male, most would agree that few more than half of all manifesting heterozygotes could possibly be identified as heterozygotes.

When a color-blind girl's father is color-normal, one knows that she has only one defect-gene. This she owes to her mother whether the latter is color-normal (but necessarily heterozygous) or color-blind because she is homozygous for one defect or a compound heterozygote for two allelic defects.

* In a letter to be published (in *Nature*), Prof. Curt Stern outlines a mechanism whereby any or all of Nowakowski's K+ color-blinds could be *homozygous* even with heterozygous mothers provided they developed from XX eggs fertilized by Y sperms.

When however a color-blind girl's father is color-blind and her mother is color normal, the girl may be a manifesting heterozygote but it will be practically impossible to prove it unless she eventually produces a color-normal son. She might have any number of color-normal brothers, but they will not be enough to prove her mother to be homozygous normal. Nor can the girl be proved to have two different (but allelic) defect-genes, for her mother cannot be proved to have given her one even if she did indeed have one to give.

For every 8 fathers who have red-green color blindness, there are 15.44 mothers who are heterozygous for some one defect. A girl is about twice as likely to have a carrier mother as to have an affected father, but while she could not escape the father's defect-gene, she has only a 50% chance of receiving her mother's. So a heterozygote (manifesting or not) is just about as likely to owe her color blindness gene to a color-normal mother as to a color-blind father. Of all manifesting heterozygotes, the *ca.* 50% who have heterozygous mothers and color-normal fathers are the ones readily identified. The *ca.* 50% who have color-blind fathers and homozygous-normal mothers and who themselves have had no color-normal sons cannot be *known* to be heterozygotes. However interesting the features of their defects may be, they must inevitably go to waste as research data.

It is not necessary to compile here all ancient and modern reports of color-blind females interpretable as manifesting heterozygotes, merely to pile up proof that such females exist. Even long ago, there seemed no doubt of that (Franceschetti, 1929; Schmidt, 1934). If new doubt now seems to arise as to whether all old descriptions of color-blind women with color-normal fathers were really concerned with XX females, one can still point to old reports of normal sons born to such women, who, to be fertile, must have been XX. (An XO mouse is a fertile female; an XO human is not.)

There is one thing unsatisfactory about the older reports. The defective persons were almost always merely identified as "red-green blind" or as deuteranopic, protanomalous, etc. by means of at most one or two tests, such as an anomaloscope or pseudoisochromatic charts. It is impossible to tell whether their defects were ***regular*** or not (and this is also true of the color-blind XY pseudofemales, and XO Turner females who are being found currently).

The few cases to be detailed here have been selected because they are contemporary. They have something more in common. They are all "remarkable" not only genetically but physiologically. They have therefore received close study (revealing their defects to be irregular) instead of being forced into one of the orthodox pigeonholes and dismissed as they would have been in the past. Their common irregularity has so impressed me that I expect that the next manifesting heterozygote to be identified will also prove to have a defect somewhat different from that which her gene would produce in a homozygote or in a male. Conversely, I am highly suspicious that one or two other "irregular" females in my ken are each heterozygous for some one orthodox gene, although I cannot yet prove that they are.

In short, one purpose of this paper is to offer the hypothesis that in manifesting heterozygotes close study of the color defect itself will show it to differ in important features from the standard defect which at first glance it seems to be. My experience with Case 1 (above) leads me to think that the color defects of all XO- and XY-"females" also deserve careful scrutiny, for it may be that when one gene produces conspicuous color deficiency in *any* female body, it has actions somehow different from those it has in a male body or, in double dose, in a female. I further believe that these one-gene-female actions may always be of such nature that the visual cells themselves are spared, but this is not the place for a full development of the basis for that belief.

Some investigators, commencing with Franceschetti (1929), have offered evidence

that a single color-defect gene in a female can be caused to "manifest" by the presence of a gene for some other sort of defect, e. g., Stargardt's disease. The evidence for mutual penetrance and/or expression-increasing effects of color-blindness genes is not voluminous. Some such effects may have occurred in some persons in the complex pedigree of Crone (1956) (although the atypically achromatic mother and son there are probably orthodox deuteranope-tritanope combinations). Clear interactions were claimed to have occurred in the famous pedigree of Jaeger (1951), where two sisters were respectively protanopic and deuteranomalous (irregularly!) although each was only heterozygous for both defects (Walls and Mathews, 1952).

The first of these contemporary and startling cases to come to my attention was Case 2 (=Ba. L. of Walls and Mathews). One of a pair of twins whose monozygosity can be attested serologically and otherwise by Dr. Charles W. Cotterman, Case 2 is an apparent protanope. Her sister is completely color-normal. So is the father and the mother and two of her brothers, but a third maternal uncle is a typical protanope. The mother and the twins all show Schmidt's sign, a depression of luminosity in the longwave half of the spectrum which two or three out of four heterozygotes for protanopia or protanomaly show as a carrier state (Schmidt, 1934, 1955; Walls and Mathews, 1952). Beyond this, Case 2 is a true dichromate, with a neutral point exactly at the protanopic average wave-length value.

Were Case 2 a genuine protanope, her retina would lack the redness receptors and she would show the more profound depression of longwave brightness which characterizes regular protanopia. Colorwise, Case 2 *is* a protanope; brightnesswise, she is only a carrier like her twin and their mother—a paradox which can be resolved only in the suprareceptoral pathways (Walls, 1955). The protanopia gene here has knocked out the cerebral *redness* neurophysiological component of color sensations without suppressing the retinal redness *receptors,* which are thus able to contribute a Schmidt's-sign magnitude of brightness to the sensations from longwave stimuli. Here, now, is a heterozygous manifestation which on the basis of an anomaloscope or a pseudoisochromatic chart test, or even both, would be unsuspectingly recorded as protanopia.

It was Case 2 who first made me wonder whether it takes some sort of brain damage to cause a simple heterozygous color condition to "manifest." At birth she had a meningocele which was slow to recede, and she squinted quite noticeably until 8 years of age. In adulthood she retains an alternating strabismus of small angle and has at least one partially paralyzed extraocular muscle. This suggests a considerable pressure affecting parts of the brain before or during birth. The same thoughts arise about the Dionne quintuplets. They were monozygotic, and two were found to be red-green color blind (apparently irregularly) when all five were tested with Ishihara charts at 6 years 9 months and again at 7 years 5 months. All five were necessarily heterozygous, and it is perhaps no coincidence that the two who manifested a color deficiency were the same two who later exhibited epilepsy (one of them having died during a seizure in 1954). At this writing, two of the five have each borne one son. A chance score would make one of them color-blind.

Another case in point for the hypothesis of irregularity in one-gene-female defects is that of Case 3. This young woman's color deficiency has received special attention because it pertains to one eye only. Vision with the right eye is normal. Case 3 was under study off and on for three or four years by C. H. Graham and Yun Hsia. She has furnished much of the basis for a new interpretation of deuteranopia and protanopia (particularly the former), which has been appearing in a series of papers (Graham and Hsia, 1957, 1958; Walls, [1959] to be published).

Graham and Hsia want to consider the left-eyed color vision of Case 3 to be essentially deuteranopia. Her usefulness for their theorization depends upon the extent

to which it is regular. They themselves have said, however, that ". . . she did not give completely typical deuteranopic responses, particularly in hue discrimination," that ". . . her left eye does not fit a category of classical color defect," that while ". . . she is most readily classifiable as a deuteranope . . . she discriminates hues better in the blue region of the spectrum than does the classical deuteranope," on the other hand ". . . some loss in blue sensitivity seems to be added to the basic loss of green sensitivity."

These are considerable understatements. The wave-length-discrimination curve of Case 3 is nothing like that of a deuteranope, owing to a most unusual mode of variation of saturation with wavelength. She sees only the two hues yellow and blue in the spectrum, separated by a neutral point within the deuteranopic range, and she is a dichromate colorimetrically. Along with her unusual saturations she suffers very great "losses" of mesopic and photopic luminosity in all but the longwave region, whereas regular deuteranopes enjoy a demonstrable gain (over normals) in mid-spectral photopic brightness (Heath, 1958). Case 3 makes an unheard-of performance on the AO H-R-R test (first edition): although on the "red-green" plates she is almost perfectly consistently "strong deutan" (making a "protan" error only on Plate 13), she *also* earns a label of "medium blue-yellow defect, unclassified as to type" by failing to see the "X" on Plate 5 or either character on either Plate 6 or Plate 17. No deuteranope was ever found to perform so.

The "deuteranopia" of Case 3 is thus highly irregular. This is not necessarily because it is uniocular, for more regular deuteranopia has been reported uniocularly in the past. Case 3 holds a master's degree in psychology, and she herself administered tests to all available relatives. Some of these were tested further by Graham and Hsia, who have not published all of the pertinent genetic facts about Case 3 and her family. Only one maternal uncle was found to be color-defective, by Case 3 herself, and judged to be deuteranomalous on the basis of his pseudoisochromatic-chart performance (personal communication).

With a color-normal brother and two color-normal parents, Case 3 can only be heterozygous, for whatever gene her mother may have—probably the same one *her* brother shows. I believe that the irregularity is due to heterozygosity and, moreover, that the defect need not have any part of its basis in the visual-cell population itself (Walls, *American Journal of Optometry*, 1958). The one defect-gene involved is not necessarily a gene for deuteranopia. Even a gene for deuteranomaly can act so strongly in a heterozygote as to knock out completely one of the three chromatic sensory components, as the next case will show.

The excessively rare form of total color blindness that is called "atypical" because the victim has normal or supernormal visual acuity (and no nystagmus or photophobia) is theoretically most readily explained as the result of the simultaneous inheritance of tritanopia (an autosomal incomplete dominant) and either protanopia or deuteranopia (Pitt, 1944). When R. A. Weale surveyed the readership of the London *Sunday Express* by means of two special articles placed therein, he learned of five atypical achromates and was able to make complete studies of three of them, a Mr. Jackson (whose visual acuity was 6/3!), a Mr. Barclay, and a Mrs. Grant (=J. G. in Weale, 1953).

The familial facts given for Jackson and Barclay make it clear that each could be a tritanope-protanope or else a tritanope-deuteranope. With Mrs. Grant (whose visual data also set her off in little ways) it was otherwise. She could not escape a protanomaly gene from her proved-protanomalous father. Her two daughters were untestably young, but her one son was deuteranomalous. Mr. Grant, although color-blind in an undiagnosed way, could not have influenced this son, whose gene must have come through Mrs. Grant from her color-normal mother.

Mrs. Grant's total color blindness therefore resulted from the joint presence of one gene for protanomaly and one gene for

deuteranomaly. She is not known to have suffered any prenatal or parturitional traumas, although "apparently she was a difficult baby during the first three months of her life" (Weale, personal communication). Unless it be claimed that each gene had a special action because the other gene was there, one has to say that this nonallelic compound heterozygote manifests a highly irregular protanomaly (the gene knocking out redness completely, as one protanopia gene has done in Case 2) and also a highly irregular deuteranomaly (the gene knocking out greenness completely, as a deuteranopia gene has presumably done in Case 1). Left with but one chromatic componential mechanism, Mrs. Grant is, of course, totally color-blind.

Evidence also happens to be available that the genes' actions in Mrs. Grant have been upon pathways and not upon receptors. Weale concluded thus from his own findings, but stronger evidence amounting to proof came from the work of Fincham (1953) upon Weale's three achromates. In experiments on the chromatic-aberration factor in the accommodation reflex, Fincham was able to tell that in protanopes and deuteranopes the receptor layer of the retina is abnormal, whereas in anomalous trichomates and in Mrs. Grant the basis of the color defect must lie above the retina. The force of this, as evidence that heterozygous actions produce only pathway defects, is weakened by the fact that Weale's two male achromates performed just like Mrs. Grant in Fincham's situation. Their retinas could lack blueness receptors under the influence of tritanopia genes and Fincham would not have known it, for in the normal retina the accommodation reflex is triggered from a spot which contains no blueness receptors. But if either a protanopia gene or a deuteranopia gene is involved in either man and is leaving the redness and greenness receptors normal, its action must be irregular. Perhaps Jackson and Barclay really demonstrate that color-blindness genes can have purely pathway effects even in a male and are more likely to do so if the person is a compound.

It is possible that every case of atypical achromasy is more or less unique. We may be wrong in expecting every protanopia-tritanopia and deuteranopia-tritanopia compound to be an atypical achromate, and perhaps we should not be so surprised upon finding an atypical achromate who could not possibly be just a compound, but with one male in every 50 a protanope or a deuteranope and one person (of either sex) in every 13,000-to-65,000 a tritanope (Wright, 1952), at least one male in every 3,250,000—perhaps one in 650,000—"should" be an atypical achromate. Where are they all?

Summary

The discrepancy which must exist between theoretical and accurately observed numbers of "red-green color-blind" females is attributable (in unknown moieties) to manifesting heterozygotes and to XO or XY females with gonadal dysgenesis or testicular feminization and to possible occasional misinterpreted mothers of XXY Klinefelter's-syndrome sons. Kallmann's theory of a common cause of color blindness and eunuchoidism is analyzed and rejected. The incidence of color blindnesses in human intersexes should be the same as in normal persons having the same numbers of X-chromosomes.

A "deuteranopic" female, reported earlier as a manifesting heterozygote but later learned to be a chromatin-negative case of gonadal dysgenesis, is described, and the irregularity of her color defect is emphasized.

Several contemporary manifesting heterozygotes for red-green color blindnesses are described. One has a color-normal monozygotic twin sister; one has one color-normal eye; one is totally color-blind. It is pointed out that the conspicuousness of these cases led to their being studied carefully enough to reveal that their defects are irregular, i. e., not the same defects the same genes would produce in males.

The hypothesis is offered that when one red-green defect-gene produces color deficiency in a female body, the defect may

always be irregular whether the sex-chromosomes present are XX, XO, or XY. It is suggested that an investigator who finds an irregular color defect in a female should look to see whether "she" may be an XX heterozygote or an XO or XY hemizygote, and it is urged that an investigator confronted with a color-blind heterozygote or a color-blind XY or XO female should look to see whether the color defect is irregular.

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Trachoma Infection in a Human Volunteer Produced by Egg-Cultured Virus

H. BERNKOPF, M. NISHMI, B. MAYTHAR, and I. FEITELBERG, Jerusalem

Successful cultivation of trachoma virus has recently been announced by T'ang et al.[1] Their claim has been confirmed by Collier and Sowa,[2] who reported the isolation of 10 strains of trachoma virus from West Africa and the successful inoculation of a human volunteer. Strains of virus have since been isolated also by American workers in Saudi Arabia.[3] The present communication reports the isolation of a strain of virus in the Middle East and the clinical picture produced in a blind volunteer.

Scrapings of the tarsal conjunctiva from seven trachoma patients, suspended in broth saline containing 1,000μg. of streptomycin per milliliter were inoculated in the yolk sac of groups of five 6-day-old chick embryos. One egg inoculated with material from Patient 1 was found dead 10 days later. A suspension of the yolk sac, bacteriologically sterile, was passed on in 6-day-old embryonated eggs, producing regularly death of the embryo five to eight days after inoculation. Nine successful passages have been carried out so far. In smears of the yolk sac, coccoid bodies of the size and staining characteristics of viruses of the psittacosis-lymphogranuloma group were regularly found. Cultivation of infected yolk sacs on a variety of bacteriological media always gave a negative result.

Patient 1, from whom the virus strain was obtained, was a 5-month-old child of a Jewish-Morrocan family, resident two and one-half years in Israel. He suffered from Trachoma I. The parents showed cicatrized trachoma with pannus; four siblings, active trachoma with pannus.

From yolk sacs of the fifth egg passage, particularly rich in viral elements on microscopic examination, a 20% suspension was prepared in broth saline and centrifuged for 10 minutes at 1,000 rpm. Titration of the supernatant indicated that it contained more than $10^{8.5}$ egg infectious doses per milliliter. This fluid was used to inoculate a human volunteer. A suspension from normal yolk sacs similarly prepared served as control material.

The 17-year-old blind volunteer showed healthy conjunctivae and clear corneae. Bacteriological examination of the conjunctivae of both eyes showed nonvirulent Staphylococcus pyogenes var. albus, scrapings from both eyes normal epithelial cells.

The suspension of the infected yolk sac was lightly rubbed with a swab into the conjunctiva of upper and lower lids of the right eye. The left eye was treated similarly with normal yolk-sac suspension. The eyes were covered with separate shields.

Two days later the right eye (inoculated) became severely inflamed with lid swelling and profuse discharge. This condition, in a less degree, has remained during the 34 days of observation. Follicles started to appear on the fourth day and have since progressively increased. On the 16th day conjunctival swelling at the upper limbus

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Virology Laboratory, The Hebrew University-Hadassah Medical School (Mr. Bernkopf and Mr. Nishmi), and Department of Ophthalmology, Hadassah University Hospital (Mrs. Maythar and Mr. Feitelberg).

and on the 25th day definite pannus were present. The control eye remained normal throughout. Blood cell counts and sedimentation rates remained within normal limits.

Epithelial scrapings were taken from the conjunctiva every second day and from the cornea on the 16th day after inoculation and examined for Halberstaedter-Prowazek bodies with Giemsa-May-Gruenwald stain. On the sixth day a few epithelial cells showed initial bodies; on the following day typical inclusion bodies containing viral elements in a carbohydrate matrix were found and have since become more abundant. They were also found in the corneal epithelium. Epithelial scrapings taken on the 16th day were inoculated into eggs, in which again virus growth was obtained. Histological examinations of follicles showed four to five layers of epithelial cells and diffuse infiltration with lymphocytes and plasma cells.

Details of further clinical and laboratory studies will be reported later.

Hadassah Medical Association, Box 499.

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The Management of Infantile Glaucoma

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An invitation to give the Mark J. Schoenberg Memorial Lecture confers with it a great honor and at the same time a profound obligation. Dr. Schoenberg was a man of great foresight and imagination. He made numerous original contributions to ophthalmology but is best known for his work in glaucoma and the prevention of blindness. Because of Dr. Schoenberg's great interest in these two phases of ophthalmology, I have chosen "The Management of Infantile Glaucoma" as the topic for my lecture this evening.

Material for this presentation has been derived from experiences with infantile glaucoma over a period of nearly 13 years. During that time, I have had the opportunity of operating upon 176 eyes of 108 children. These patients have been sufficiently well studied and followed long enough to permit certain analyses and conclusions. No attempt will be made to review the literature completely, because this was done recently in the report [1-5] of the Symposium on Infantile Glaucoma, 1954.

I wish at the outset to acknowledge the work of the late Dr. Otto Barkan,[6,7] whose adaptation of goniotomy for the treatment of infantile glaucoma has proved to be epoch-making. His successful results and our own very poor results, with the use of conventional surgical techniques, at the Hospital of the University of Pennsylvania prior to this time served as incentive for the efforts that have resulted in the subject matter of my lecture tonight. I first employed goniotomy in 1946, and published the results,[8] in a small number of eyes, in 1949. These were in agreement with those of Barkan. The present report includes all eyes accumulated to date upon which I have been able to do either the first operation or which were relatively unmutilated by previous operative procedures when first seen by me. Eyes which had been operated on several times with distortion of normal anatomy which precluded the possibility of a good operative result were not included.

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From the Departments of Ophthalmology, Hospital of the University of Pennsylvania and the Children's Hospital of Philadelphia.

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Diagnosis

Although infantile glaucoma is considered to be a rare disease, its gravity is indicated by the number of children still being admitted to schools for the blind with loss of vision due to this cause. The estimates vary from 5% to 13%. New operative methods can reduce the figure tremendously, but, in order to do so, the diagnosis must be made and the treatment instituted before the eye has been badly damaged by the glaucomatous process.

Infantile glaucoma can present difficulties in diagnosis fully as great as in primary glaucoma of the adult. When classical signs of the disease are present, the diagnosis is usually easy. These signs consist of photophobia, haziness of the cornea, corneal enlargement, ruptures in Descemet's membrane, and a definitely elevated intraocular pressure. However, these signs may be absent, and the diagnosis may be possible only after repeated examinations with measurements of ocular tension. The ophthalmologist's clinical judgement can be tested to the utmost.

The disease may be present at birth and the diagnosis obvious, or it may become ap-

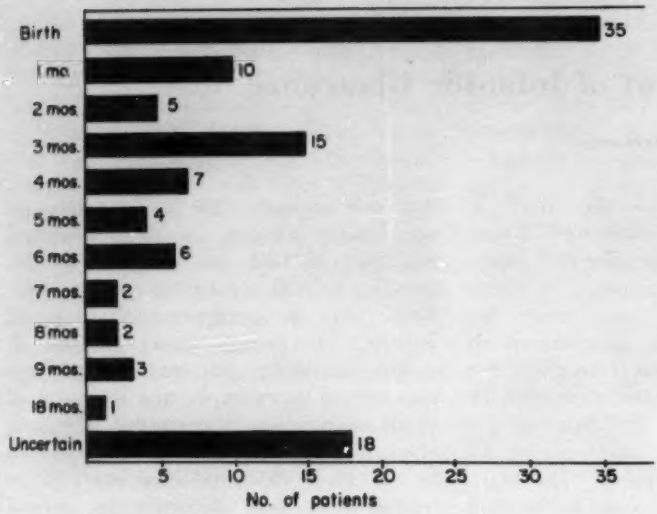

Fig. 1.—Age of recognition of infantile glaucoma in 108 patients.

parent only after months or years and offer serious diagnostic problems. In Barkan's [9] series of patients, the disease was found at birth in 35%. Gros [10] reported its presence in 60% at birth. In the remainder of his patients, the diagnosis was made in 13.3% by the end of the first year, 17.7% between the first and third years, and 8.8% after 3 years of age. Anderson,[11] in summarizing the papers by Seefelder, Detterming, Stolting, and Fleischer, quoted the following statistics:

Present at or before birth in 102 (40%)
Present at 6 months or under in 86 (34%)
Present at 1 year or under in 30 (12%)
Present at 6 years or under in 28 (11%)
Present at over 6 years in 5 (2%)
Unreliable or no information.

In the present series of 108 patients, the diagnosis was made at birth in 35 (31%) and noted after birth in 73 (69%) (Fig. 1). The initial symptoms in these two groups of patients are of considerable interest. In infants born with the disease, the diagnosis was usually suggested by clouding of the corneas and enlargement of the eyes (Table 1). In the 73 eyes where the disease became apparent at some time after birth, the initial symptom was noted in 56. In 23 of these, photophobia was the first sign noted, occurring before the cornea became enlarged or cloudy. The statement, therefore, can be made that any child under 2 or 3 years of age, and particularly during the first year, who has unexplained photophobia and tearing must be suspected of having infantile glaucoma. The importance of photophobia as a diagnostic sign is emphasized by the need for early operative intervention before enlargement of the eye and resultant poorer visual outlook occurs.

Photophobia, also, is an excellent criterion for operative success or failure, because it usually clears promptly with normalization of tension. When operation is unsuccessful, photophobia usually persists, even though at times the cornea may have cleared.

TABLE 1.—*Initial Sign in 108 Patients with Infantile Glaucoma*

Sign	Noted		Total
	At Birth	After Birth	
Large eyes (4)	8	7	15
Cloudy cornea (12)	15	18	33
Large eyes & cloudy corneas (1)	6	8	14
Photophobia & tearing	4	23	27
Uncertain	2	17	19
Total	35	73	108

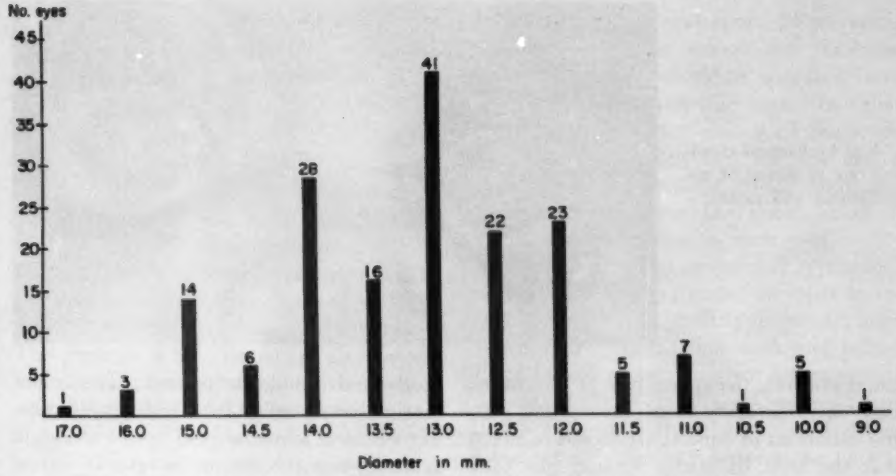

Fig. 2.—Range of corneal diameter in 176 eyes (108 patients) with infantile glaucoma.

A large corneal diameter is an important diagnostic sign but is far from infallible. It is impossible to be arbitrary about the normal corneal size, but when the diameter is over 12 mm. the diagnosis of infantile glaucoma must be excluded. However, a corneal diameter of less than 12 mm. gives no positive assurance that the patient might not have the disease. In the present series, corneal diameters were 12 mm. or more in 155 of the 176 eyes and under 12 mm. in 21 eyes (Fig. 2). The corneal diameter should be measured at the time of each examination, because an increasing corneal diameter is almost certain evidence of the disease. Measurements of corneal diameter are also of value in evaluating surgical therapy, since enlargement ceases after normalization of tension.

Corneal haze is limited to the epithelium when it first appears, as Barkan [3] has shown (Fig. 3). He demonstrated that the cornea can be cleared to permit goniotomy through a contact lens, by gently curetting the edematous epithelium from the cornea. As the disease advances, the edema also involves the stroma, and the cornea may become practically opaque (Fig. 4). Still later fibrous scarring may occur, and the opacity becomes irreversible. Until scarring occurs, clearing of the cornea after normalization of tension is remarkable. Seemingly opaque corneas can clear with resultant normal vision. When the corneal haze is limited to

Fig. 3.—Corneal haze limited to epithelium.

Fig. 4.—Corneal clouding due to edema of the epithelium and stroma.

the epithelium, the appearance of the cornea may vary markedly from day to day with the variations in tension. It should be noted that the level of ocular tension can vary considerably, as it does in other types of glaucoma.

Another even more diagnostic sign of infantile glaucoma is ruptures in Descemet's membrane. These occur with enlargement of the cornea and stretching of Descemet's membrane under increased intraocular pressure. They occur relatively late in the evolution of the ocular signs and, in general, indicate a poorer visual result after normalization of tension than in eyes that have no ruptures.

Glaucomatous excavation of the optic nerve is of little or no diagnostic value in infantile glaucoma unless the disease is very advanced. It occurs late in the course of the disease, probably because the optic nerve is protected by the elasticity of the fibrous coats of the eye, which permits enlargement of the eyeball rather than displacement of the lamina cribrosa.

The most important confirmatory test for infantile glaucoma is the recording of intraocular pressure, but, unfortunately, pitfalls exist. The tension should be recorded with the child under deep surgical anesthesia. The eyes should be in the primary position and no longer deviated upward, a sign that is indicative of light anesthesia. If there is any question as to a free open airway, endotracheal intubation should be carried out. The child should be breathing freely and completely relaxed. The ocular tension may measure as high as 40 mm. Hg (Schiøtz) in a normal eye if the child is struggling for air or his eye is rolling under light anesthesia. This, of course, can lead to the mistaken diagnosis of infantile glaucoma and occasionally has led to unnecessary surgical intervention. When no other objective sign of infantile glaucoma is present, one is undoubtedly well advised to defer surgery and to repeat the recording of tension in a few days. Likewise, finding normal pressure in an eye suspected of having infantile glaucoma should not lead to a false sense of security. The pressure may vary from day to day, and such factors as dehydration associated with preparing infants for anesthesia may lead to a lowered pressure. When in doubt, repeated recordings of intraocular pressure should be made, and even then the diagnosis may be difficult. Tonography has been unreliable in my own experience.

Theoretically, a large corneal diameter with large corneal curvature might lead to a false recording of ocular tension. In my experience, however, if the tension remains less than 3:5.5 weight (Schiøtz), regardless of corneal curvature, the disease does not progress.

A lack of correlation between the ocular signs of infantile glaucoma and the level of intraocular pressure is often found in infantile glaucoma. Marked corneal enlargement and corneal haze may be found with intraocular pressures of 35 to 40 mm. Hg

(Schiøtz). This is probably best explained by the inability of the infantile eye to withstand even relatively small increases of intraocular pressure.

Differential Diagnosis

The large cornea of infantile glaucoma must be differentiated from megalocornea, high myopia, Hurler's disease, and congenital idiopathic edema of the cornea. The differentiation from these diseases is usually easy and will not be reviewed in detail here. The findings in the myopic eye are obvious, but one must be on guard, however, because many eyes with infantile glaucoma are highly myopic. Megalocornea is present at birth. The eye is usually otherwise normal. It is usually familial and found predominately in males. It is bilateral and symmetrical. Visual function is good, and the patient usually has no symptoms. Hurler's disease is differentiated by the associated systemic signs. Congenital idiopathic edema of the cornea is evidenced by what appears to be diffuse edema of the epithelium and stroma. It is possible that the condition may represent an incomplete form of Hurler's disease. Photophobia is absent or minimal, and the corneal diameter is normal or top normal. Ruptures in Descemet's membrane are not seen. The differentiation is usually made by the repeated readings of ocular tension and the recording of corneal diameters.

Gonioscopic Picture of Infantile Glaucoma

Differences of opinion exist regarding the gonioscopic findings of infantile glaucoma. Barkan,[12] François,[13] Kluyskens,[14] Weekers,[15] and Schaeffer[1] felt that the picture is characteristic and that gonioscopy is of diagnostic value. Barkan has described a transparent membrane which overlies the trabecula and covers the trabecular area of the angle in children with infantile glaucoma. This usually has a shagreened appearance. Barkan believed that the iris usually has an anterior insertion into this membrane. From his drawings, the insertion is usually well in front of the scleral spur. However, if this were true, the scleral spur and the canal of Schlemm should be obscured from view, which is rarely the case. In other eyes, he believed that veiling of the angle wall was present but that the iris had a normal insertion into the ciliary body and scleral spur. Barkan has noted blood in the canal of Schlemm in such eyes.

In my opinion, the gonioscopic appearance of the angle of the anterior chamber in infantile glaucoma is of little diagnostic help. When I first started this work and before I had looked at many normal infant eyes, I felt that at times I could see abnormal tissue in the angle wall. However, I now feel that I can see no difference between the normal angle of the infant eye and the angle in infantile glaucoma unless the eyeball is enlarged or some other anomaly, such as aniridia, is present. The angle is open, and the iris inserts as it does in the normal infant's eye. The scleral spur is almost invariably easily visualized. Barkan[12] has noted that the angle of the anterior chamber of the infant eye is not as fully differentiated as in the adult eye. This is most apparent in the apex of the angle behind the scleral spur. The recess at the apex is minimal, and the iris seems to run directly to the corneoscleral wall just behind the scleral spur. The author has been unable to observe a real difference in this appearance between the normal eye of the infant and the eye with infantile glaucoma. The normal position of the iris can be demonstrated in the eye with infantile glaucoma by filling the canal of Schlemm with blood. The blood then appears in its usual position anterior to the scleral spur. At times, one has the impression that it is more faint than in normal infants, but it is difficult to be positive. It often fills incompletely, but that also may be true in the normal eye.

I have attempted to fill the canal of Schlemm with blood in 126 eyes with infantile glaucoma, usually after control of ocular tension by surgery (Table 2). The canal filled with blood in 116 of these eyes and failed to fill in only 10 eyes. In 25

TABLE 2.—*Incidence of Filling of Canal of Schlemm with Blood in 176 Eyes*

Fills with jugular compression	91
Fills spontaneously	25
Does not fill	10
Not done	50
Total	176

TABLE 3.—*Ocular Anomalies in Patients with Infantile Glaucoma*

	No. Patients
Congenital cataract	5
Sturge-Weber	3
Aniridia	2
Strabismus	2
Posterior embryotoxon	1
Total	13

eyes it filled spontaneously, and in 91 eyes it filled with jugular compression. In a few eyes the canals were made to fill by doing a paracentesis of the anterior chamber at the time of initial surgery, but the usual practice was to cause the canal to fill by compressing the jugular veins at the first follow-up visit, about six to eight weeks after operation. In addition to proving that the angle is open, the consistency with which the canal of Schlemm filled indicates that the canal of Schlemm usually is present in infantile glaucoma.

Anomalous vessels are more readily visualized in the eye with infantile glaucoma, but this is not surprising in an eye that first of all has other anomalies and is congested and irritable. In occasional eyes the stroma of the iris is defective. The most characteristic gonioscopic feature of infantile glaucoma is a palisade-like appearance of the pigment at the periphery of the iris (Fig. 5). The pigment periphery gives the appearance of palisades, or triangular segmentation, with the base of the triangle at the periphery of the iris. This phenomenon probably results from a stretching of the iris diaphragm as the eye enlarges with changes in the iris pigment. It can also be seen in eyes with high myopia.

Conditions commonly associated with infantile glaucoma, such as aniridia and posterior embryotoxon, have a very typical appearance and are easily diagnosed (Table 3). In the present series of patients, the angles of the patients with nevus flammeus or Sturge-Weber syndrome look like any eye with infantile glaucoma. In my experience, these eyes respond to treatment in the same way as do eyes with ordinary infantile glaucoma.

Pathogenesis of Glaucoma

The microscopic anatomy of the eye with infantile glaucoma has remained obscure because of the small number of eyes available for study. The open angle found by gonioscopic examination, presence of the canal of Schlemm, and recent tonographic data [16] suggest an obstruction to aqueous outflow in the trabecular area. This should occur on the basis of a congenital maldevelopment and, because of the lack of at least gross changes to be seen by gonioscopy, should be microscopic in nature. Another possibility rests in the corneoscleral wall peripheral to the canal of Schlemm.

Maumenee [18] has recently suggested, in his paper on "The Pathogenesis of Congenital Glaucoma," that obstruction to aqueous outflow occurs on the basis of an abnormal insertion of the longitudinal and circular bundles of the ciliary muscle into the trabecular fibers. This type of insertion tends to compress the scleral spur forward and externally, thereby narrowing Schlemm's canal. Contraction of the longitudinal muscle fibers further narrows the canal, and contraction of the circular muscle does not open the trabecular spaces.

Etiology

Heredity and maternal virus infections during the first trimester of pregnancy are probably the two most important etiologic factors in infantile glaucoma, as with any

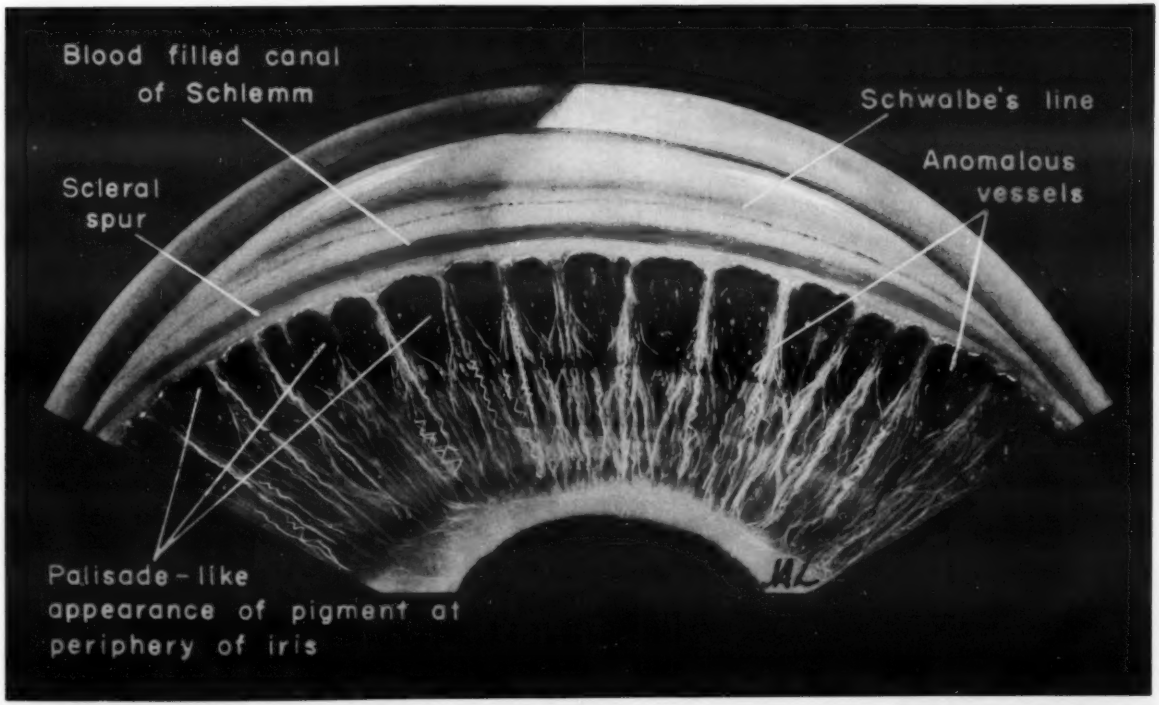

Figure. 5.—Angle of the anterior chamber of an eye with infantile glaucoma, showing palisade-like appearance at periphery of iris and canal of Schlemm filled with blood.

TABLE 4.—*Etiological Factors in 108 Patients with Infantile Glaucoma*

Family History		
Infantile glaucoma (sibling)		4
Primary glaucoma (adult)		7
Total		11
Abnormal Pregnancy		
Syphilis		2
Vaginal bleeding		5
Virus infection:		
Influenza	3	
Rubella	4	7
Toxemia		3
Miscellaneous		3
Total		20

TABLE 5.—*Systemic Anomalies in Patients with Infantile Glaucoma*

	No. Patients
Cardiac	6
Mental retardation	11
Neurological defects	4
Umbilical hernia	3
Birth marks	2
Syndactaly	2
Renal disorder	2
Anemia	1
Undescended testicle	1
Multiple developmental defects	1
Slow in physical achievements	1
Died	3
Total	37

congenital anomaly (Table 4). The hereditary tendency is recessive. In the present series of 108 patients, a definite family history of glaucoma could be obtained in 11 patients (Table 4). Four of the patients had a sibling with the disease. Two of these were identical twins. The mother of one and the father of another child had primary glaucoma. One child had grandparents suffering from glaucoma, and another has a great uncle with the disease. One patient had parents blind of an unknown cause.

Maternal abnormalities during the pregnancy are undoubtedly of importance. The mothers of seven infants in this series had suffered from maternal virus infections early in pregnancy (Table 4). The mother of another patient, not included in this series because she was operated on elsewhere, had been vaccinated for smallpox during the second month of pregnancy. Three mothers had toxemia of pregnancy, five gave a history of vaginal bleeding, two had a positive serology, and three had miscellaneous disturbances, among which were pyelitis, intestinal bleeding, and fainting spells. The ocular anomalies often are only part of a general insult to the embryo or fetus as indicated by the frequent association of abnormalities elswhere in the body (Table 5). Cardiac and neurological anomalies were most frequently found.

Prognosis

The prognosis for infantile glaucoma has been greatly improved since Barkan adopted goniotomy for its treatment. Convincing evidence has accumulated to show that useful and even normal vision can be preserved if the child can be operated on sufficiently early in the course of his disease, before visual function is impaired. This is in contrast to the statement by Anderson [11] that regardless of therapy there was little likelihood of maintaining sufficient vision into adult life to permit earning a livelihood. Kluyskens [14] pointed out that even though control of tension can be achieved in 60% of eyes, good function is achieved in only 23%.

When the pressure is not controlled, the eyeball continues to increase in size and corneal haze increases. Later, the cornea tends to clear somewhat as the children become older, and there is a tendency to stabilization in the teen-age years (Fig. 6). Deterioration of the globe, however, is progressive with marked optic atrophy. The fibrous coats of the eye become thinner, particularly at the periphery of the cornea, until final rupture of the globe occurs with even minor trauma. Other complications may occur spontaneously or on the basis of minor trauma. These include anterior chamber hemorrhage, retinal detachment, and dislocation of the lens.

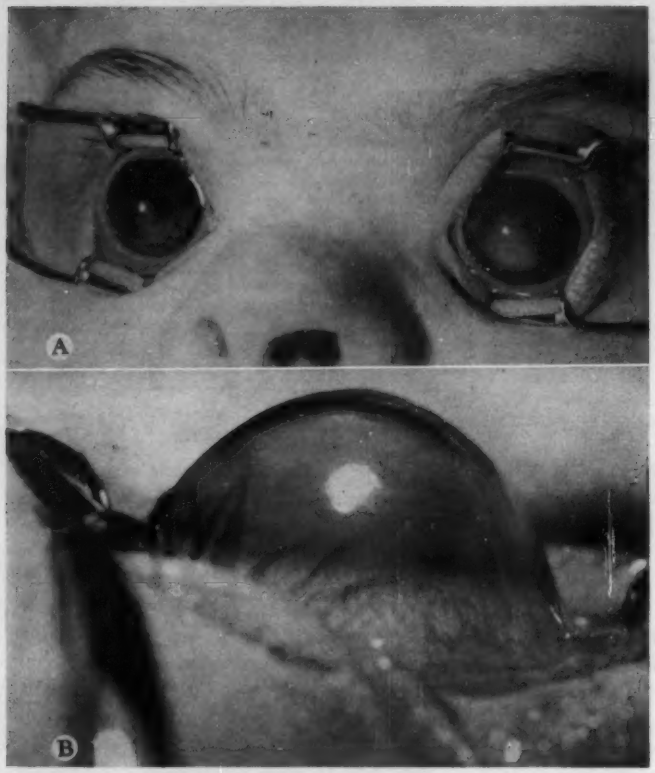

Fig. 6.—Eyes showing enlargement with advanced infantile glaucoma and residual scaring. *B*, profile of right eye.

At times, spontaneous cure of the disease may occur. These children may show later in life all of the signs of healed infantile glaucoma, including enlargement of the cornea, ruptures in Descemet's membrane, and an optic nerve that may vary from normal to excavated with atrophy, and yet have a repeatedly normal pressure with no further progression of the disease. Barkan observed this phenomena, and Anderson collected several such patients. During the 12½ years of my experience with infantile glaucoma, I have seen this in six patients. Recovery was unilateral in three and bilateral in three patients.

Treatment

The treatment of infantile glaucoma is primarily surgical. Justification no longer exists for even a trial of medical therapy, unless for investigative purposes as newer therapeutic methods are evolved. Furthermore, I believe that the period of time required for a trial of medical therapy only deprives the patient of the better visual result which might be anticipated from early surgery. My own experience with medical treatment was obtained with approximately 20 patients early in this series. The tension was not reduced sufficiently to justify continuing medical therapy in any of these eyes.

Goniotomy, goniopuncture, or a combination of the two is the operation of choice. Results from other operations historically have been very ineffective. Even after repeated operations, the end-result is usually failure because of vitreous loss, intraocular hemorrhage, subluxation of the lens, and corneal edema with permanent corneal opacity (Fig. 7). This statement has been supported by numerous authors, among whom

Fig. 7.—Blind eyes after repeated conventional filtering operations.

were Zentmayer,[17] Sugar,[19] Lister,[20] Anderson,[11] and Kluyskens.[14]

Recently cyclodiathermy has been urged as an operative procedure in the treatment of infantile glaucoma. Good results have been reported by Kluyskens,[14] Weekers and Weekers,[15] and Bailliart.[21] The experience of the participants in the symposium [8] on infantile glaucoma did not confirm those observations.

Goniotomy was described by de Vincentiis,[22] in 1893. It was originally introduced for use in all types of glaucoma. It was thought to be effective through debridement of the iris angle. Several articles appeared in the literature during the next decade, but the operation fell into disuse until Barkan took up its use for infantile glaucoma. He reported his first results in 1942,[6] and found that goniotomy controlled the tension in a significant number of eyes. In 1949, I reported [8] comparable results in a series of 16 eyes with infantile glaucoma, all operated on by goniotomy. Several papers since that time have corroborated its effectiveness, including those by Callahan,[23] McArevey,[24] McKinney,[25] Robertson,[26] Wilson,[27] Hertzberg,[28] Algan,[29] Bietti,[30] Lister,[20] and Paufique.[31]

Barkan was convinced that goniotomy exerted its effect by incision of elements responsible for the anterior insertion of the iris in the trabecular area with establishment of normal outflow of aqueous into the canal of Schlemm. Some such explanation is particularly reasonable in infantile glaucoma, where the canal of Schlemm can be demonstrated to be present in a very high percentage of eyes. However, in my experience the plane of the iris has a normal relationship to other structures of the angle, and any abnormality of insertion must be attributed to possible abnormal extension of uveal tissue overlying the trabecula or possibly, as Maumenee [18] has recently suggested, due to an abnormal insertion or extension of the longitudinal muscle. If either mechanism is assumed to be correct, goniotomy could be effective by incising or removing this tissue. However, goniotomy could not possibly be effective in eyes where the canal of Schlemm might be congenitally absent or in eyes with advanced disease and marked enlargement of the globe where the canal can become obliterated, as pointed out by Anderson.[11]

Goniopuncture (1955) might in such eyes have a better chance of being effective than goniotomy because it is a fistulizing procedure. This operation was first developed after accidental perforation of the corneoscleral wall, while doing a goniotomy in a 19-year-old girl with advanced juvenile glaucoma. A cleft in the trabecular area was seen by gonioscopy, and edema of the overlying conjunctiva was observed by slit-lamp microscopy. After observing this eye, a technique was developed by which a goniotomy, or a specially devised goniopuncture, knife was carried across the anterior chamber and a counterpuncture was made through the trabecular region of the oppo-

site angle, causing a fistula into the subconjunctival space. The operation was found to be ineffective in patients over 30 years of age, but in patients under 30 years and including those with infantile glaucoma, control of tension could be accomplished in a significant number of eyes. The effectiveness of goniotomy and goniopuncture in infantile glaucoma, when compared by doing one procedure on one eye and the other on the fellow eye, was comparable. Either procedure could be effective as a primary procedure in about 50% of patients, although goniotomy seemed to be the more effective. Other reports of its successful use include those of Robertson,[32] Moore,[33] Weisser,[34] Robertson,[35] and Tyner and Swets.[36]

The fact that goniopuncture could give results at least comparable to goniotomy suggested that goniotomy also might exert its effect by creating fistulae in the angle wall. The corneoscleral wall of eyes with infantile glaucoma is extremely thin, and it might be argued that perforation could easily result from the passage of a goniotomy knife around the circumference of the angle, but definite proof has not been obtained to this time. Because the two procedures theoretically do have a different mechanism, I began to combine them into a single operation. A goniotomy is done, and at the end of the sweep of the goniotomy knife, a puncture is made through the corneoscleral wall. This offers the advantage of each procedure and seems to give better results than either operation done alone.

Technique

Goniotomy.—Goniotomy is done with the infant under surgical anesthesia. A speculum is inserted, and the eye is grasped in the horizontal meridian at the nasal limbus by a fixation forceps. A preliminary oblique knife-needle puncture, as described by Chandler,[37] is made in the upper temporal quadrant to permit prompt restoration of the anterior chamber. Saline solution is injected through this opening after completion of the operation to aid in restoring the anterior chamber. This is desirable to help prevent the formation of an anterior peripheral synechia along the goniotomy incision. Saline is preferable to air because it does not produce a pupillary block, which would close the fistula. A goniotomy knife is inserted through the cornea approximately 2 mm. within the temporal limbus in the horizontal meridian and carried across the anterior chamber into the opposite angle. I do not use a gonioscopic lens for the procedure because it is cumbersome, makes the operation more difficult, and does not seem to alter the results. A direct view of the angle is not essential, if one has a thorough knowledge of gonioscopy and the gonioscopic anatomy of the angle. A correct position of the knife in the angle is insured if the knife is carried across the anterior chamber in such a way that the tip is directed at the junction of clear cornea and sclera, as if making a counterpuncture for a cataract section that would be too deep. When the knife is inserted in this manner, the tip is invisible as the eye is viewed anteriorly. With the tip in the blind portion of the angle and not engaged with iris, it follows that the incision must be made in the trabecular area, since the trabecula extends from Schwalbe's line to the scleral spur. Sweeping the knife along the angle is not difficult, for the knife is guided somewhat by the inner scleral sulcus. In the right eye, the knife is inserted in the 9 o'clock meridian and the sweeping incision started in the angle at the 5 o'clock position. It is extended upward as nearly as possible to the 1 o'clock meridian. The knife is then withdrawn, keeping the blade away from the pupillary space and over the iris, which helps to prevent injury of the lens. Upon completion of the incision some bleeding usually occurs, but care is taken to prevent clot formation in the anterior chamber by gentle continuous irrigation with saline until all bleeding stops. A blunt No. 27 gauge needle or a lacrimal cannula attached to a 2 cc. syringe is inserted into the opening made by the goniotomy knife but

not into the anterior chamber. Fluid is directed into the chamber, which promptly regurgitates, removing the blood. Bleeding usually stops within a minute or two, and, for some reason, secondary bleeding rarely occurs. Pilocarpine is instilled to help retract the iris away from the angle, and the anterior chamber is filled with saline. Both eyes are patched.

Goniopuncture.—The operation is done under general anesthesia. A speculum is inserted. In adults an oblique puncture is made through the upper temporal part of the cornea for refilling of the anterior chamber. This is not done in infants because the corneoscleral wall is so thin that saline or air is not retained. Instead they flow beneath the conjunctiva and Tenon's capsule where they exert pressure on the globe and tend to prevent reformation of the anterior chamber. The conjunctiva overlying the area where the puncture is to be made is ballooned outward away from the globe by the subconjunctival injection of saline solution to help prevent perforation of the conjunctiva by the knife. A goniopuncture or goniotomy knife is introduced through clear cornea 1 to 1.5 mm. within the limbus at approximately 9:30 o'clock in the right eye or at 2:30 o'clock in the left eye and directed nasally toward the 6 o'clock meridian. The blade is introduced flat, on a plane parallel with the iris, and the tip is carried across the chamber until it reaches the trabecular region of the opposite angle. It is then thrust forward through the corneoscleral wall until the blade of the knife is visible beneath the previously ballooned conjunctiva. It is then pulled back into the anterior chamber and withdrawn from the eye.

A Barkan goniotomy knife is better for goniopuncture in infants than the specially designed goniopuncture knife which is used for adults. The goniotomy knife makes a smaller opening in the corneoscleral wall, which is desirable in glaucomatous infant eyes because of the very thin corneoscleral wall. Furthermore, to insure a small puncture opening, the knife should not be rotated in the subconjunctival space, as is advised in adults for the purpose of a larger fistula. The puncture through the trabecula should be only a puncture, and temptation to enlarge it as the knife traverses the corneoscleral wall must be resisted. A larger opening leads to incarceration of the iris, with plugging of the fistula. Occasionally, bleeding occurs at the time of the puncture but usually causes no difficulty if the blood is washed from the anterior chamber as it appears. This is easily accomplished by inserting the tip of a blunted No. 27 gauge needle into the opening at the site of entrance of the goniopuncture knife into the anterior chamber. Pilocarpine is instilled to retract the iris away from the site of the puncture. Both eyes are covered for 24 hours.

Combined Goniotomy-Goniopuncture.—Detailed description of the technique is unnecessary, because the operation is accomplished simply by doing a goniopuncture upon completion of the sweeping incision of a goniotomy.

Postoperative Management.—Postoperative care after goniotomy and goniopuncture, alone or combined, is relatively simple. The anterior chamber has usually re-formed the morning after surgery, and no further dressings are needed. Local steroids combined with antibiotics are instilled four times daily for a few days. Atropine is used only if the eye shows marked reaction, but it is rarely indicated. The two most worrisome postoperative complications are hyphemia and infection. Although some hemorrhage into the anterior chamber is the rule at the time of operation, recurrent hyphemia is rare. In a total of 247 operations for infantile glaucoma, massive hyphemia with bloodstaining of the cornea occurred in only three eyes. This is surprising, in view of the frequency of recurrent hemorrhage following traumatic hyphemia. Only one postoperative infection resulted. This consisted of a corneal abscess due to pyocyaneus (Pseudomonas aeruginosa) at the site of entrance of a goniotomy knife. A severe corneal opacity

resulted, but the tension was normalized. The patient is usually discharged from the hospital on the third to the fifth postoperative day.

Follow-Up.—The patient is readmitted to the hospital in six to eight weeks for reexamination under general anesthesia. If reoperation is necessary, it is done at that time. Reexamination before this time can be misleading, because the tension can remain elevated for three weeks or longer and become normal later. If the tension is normal and the cornea clear at the first postoperative check up, reexamination under anesthesia is usually done at three and six months and then at yearly intervals for two or three years. When the tension is controlled, clouding of the cornea, photophobia, and tearing usually subside within the first three or four weeks after operation. When the eyes have done well for three months, recurrence is rare. The corneal diameter is measured at each follow-up visit under anesthesia and the optic nerve carefully observed. When the child has become older, any change in the appearance of the amount of cupping of the optic nerve is an indication for reexamination under anesthesia. The recording of ocular tension can often be done in the ophthalmologist's office, beginning at the age of 4 years. General anesthesia, after one year of age, presents formidable psychological problems. To allay fear, the child should be heavily sedated or preferably also given rectal thiopental (Pentothal) before being taken to the operating room. If not carefully managed, severe psychological trauma can result. Cooperation in follow-up examinations of these children is usually excellent because of the great concern of the parents.

Results.—The series of 176 eyes reported in this paper is the third large series reported in the literature operated upon by angle surgery. Barkan,[38] in 1953, reported his results in 196 eyes (121 patients), all operated on by goniotomy. The tension had been controlled in 80% of 188 eyes where follow-up was complete. Haas,[4] at the symposium on congenital glaucoma, analyzed the results in 329 eyes (202 patients), but this group included 210 eyes operated on by Barkan, as well as eyes operated on by Schaeffer, and by Haas himself. The results in the three series are more or less comparable. Goniotomy was done on 253 of the eyes reported by Haas, with control of pressure in 77%. Of 329 eyes reported by Haas, 17 eyes had been operated on by goniopuncture, 22 eyes by combined goniotomy and goniopuncture, and 30 eyes by miscellaneous procedures. The ocular tension had been controlled in 10 of the 17 eyes operated on by goniopuncture. Goniopuncture and goniotomy were done as a combined procedure in 22 eyes, with control of pressure in 15 eyes.

In the present series of 176 eyes, adequate follow-up information was available in 169 eyes. All patients have been followed for longer than three months and the vast majority for many months and as long as 12½ years. Information on some of the patients has been obtained through the referring ophthalmologist. The tension was controlled by angle surgery, including reoperations, in 145 eyes (85.8%) (Table 6). Adequate follow-up data was not obtained in five eyes. On two more eyes of a patient with Sturge-Weber disease, low-voltage irradiation was given over the ciliary body too soon after the operative procedures to permit a decision as to which was curative. In all probability, the goniotomies were the effective measures.

It seemed of considerable interest to compare the effectiveness of goniotomy and goniopuncture as a primary procedure (Table 7). Goniotomy was, therefore, done on 21 eyes as a primary procedure and

TABLE 6.—*Over-All Results from Goniopuncture and Goniotomy Alone or Combined in 176 Eyes (108 Patients) with Infantile Glaucoma*

Success	145
Failure	24
Doubtful	2
Inadequate follow-up	5
Total	176
Percentage successful	85.8

TABLE 7.—*Results from First Goniopuncture or Goniotomy Alone or Combined in Infantile Glaucoma*

	Success	Failure	% Successful
Goniotomy	13	8	62
Goniopuncture	21	23	48
Combined	86	18	82
Over-all % successful			71

TABLE 8.—*Results from Reoperations with Use of Goniopuncture and Goniotomy Alone or Combined in Infantile Glaucoma*

Operation	Success	Failure	% Successful
Second	12	27	30
Third	8	9	47
Fourth	1	6	14
Fifth	0	4	0
Sixth	0	2	0
Seventh	0	2	0

successfully controlled the pressure in 13 eyes (62%). Goniopuncture was done as a primary procedure in 44 eyes with control of pressure resulting in 21 (48%). When both eyes were affected goniotomy was done on the better eye, since it was the more conventional procedure. The relatively small number of patients in these two series lend little significance to the actual percentage. However, it can be stated with certainty that both goniotomy and goniopuncture could control the ocular tension in infantile glaucoma when done as separate procedures.

Goniotomy and goniopuncture combined into one operation seemed to give better results than when either procedure was done alone. This operation was done as a primary procedure on 104 eyes. The ocular tension was controlled in 86 eyes (82%), and the number of reoperations were fewer. This suggests an additive effect and a separate conclusion for goniotomy and goniopuncture. If each exerted its effect by causing a fistula, it is doubtful that their combination would be more effective than either alone.

Goniotomy and goniopuncture alone or combined are less effective after the first operation has failed, and after three or four operations the chance of success rapidly diminishes (Table 8). In this series of patients, these procedures were effective in only 33% when done as a second operation, 47% as a third operation, and 14% as a fourth operation. With this evidence, one should probably employ some other operative technique, if angle surgery fails on three or four occasions. Unfortunately no other operation has much to offer (Fig. 8).

Factors responsible for success or failure were evaluated. Somewhat surprisingly, there seemed to be no correlation between corneal diameter and control of tension, because angle surgery seemed almost as effective in eyes with large corneal diameters as those with small diameters (Table 9). There was, however, a definite correlation between corneal diameter and visual acuity (Table 10). Visual results were found to be good if the corneal diameter is not over 13 mm. and much poorer

Fig. 8.—Bilateral failure from repeated goniotomy-goniopuncture followed by other types of procedures.

TABLE 9.—*Correlation of Corneal Diameter with Control of Intraocular Pressure by Goniotomy and Goniopuncture Alone or Combined*

Corneal Diameter, Mm.	Success *	Failure *
17.0	0 (0)	1 (100)
16.0	3 (100)	0 (0)
15.0	10 (77)	3 (23)
14.5	5 (83)	1 (17)
14.0	20 (74)	8 (26)
13.5	16 (94)	1 (6)
13.0	38 (95)	2 (5)
12.5	16 (84)	3 (16)
12.0	18 (78)	5 (22)
11.5	5 (100)	0 (0)
11.0	7 (100)	0 (0)
10.0	7 (100)	0 (0)
Total	145	24

* Figures in parentheses are percentages.

if more than 13 mm. The vision could be determined in 29 eyes with a corneal diameter of 13 mm. or less. All except 4 had a visual acuity of 6/22 or better, and 14 of them had a visual acuity of 6/9 or better. In 24 eyes where the corneal diameter was 13.5 mm. or more, 15 eyes had a visual acuity of 6/30 or less. The reasons for the poorer visual results were permanent corneal opacities, ruptures in Descemet's membrane, amblyopia, high myopia, or damage to the optic nerve. The poorest prognosis seemed to be in those infants born with large eyes and cloudy corneas, where extensive damage to the eyes and corneas had occurred by birth. These findings emphasize the need for early surgical intervention before ocular damage results.

Correlation of visual result with the age of onset was examined, but none was found (Table 11). Neither was any correlation between age of onset and the control of ocular tension demonstrated. Haas had found that the results were considerably better during the first two months of life, but our series of patients does not bear this out.

The most annoying operative complication was hemorrhage. This is managed by gentle continuous irrigation to remove the blood before it clots. Recurrent hemorrhage postoperatively is extremely rare. Only three patients in this series had such massive hemorrhages as to result in bloodstaining in the cornea. A traumatic cataract was encountered in one patient. One patient developed a pyocyaneous abscess of the cornea at the site of entrance of the goniopuncture knife. The tension was controlled, but permanent corneal opacity remained (Fig. 9). Another patient developed an odd type of atrophy of the iris with absorption of pigment along the area of the goniotomy (Fig. 10). Whether this was a denervation effect or was caused by interference of blood supply of the iris could not be determined. Only four patients in this entire series, where goniotomy and goniopuncture

TABLE 10.—*Correlation of Visual Result with Corneal Diameter in Infantile Glaucoma*

Corneal Diameter, Mm.	Visual Acuity												
	6/5	6/6	6/7.5	6/9	6/12	6/15	6/18	6/22	6/30	6/60	6/100	CF	LP
17.0													
16.0												1	
15.0				1					1	2		1	
14.5					1							1	
14.0		2		2	2					1	2	3	2
13.5						1							1
13.0	1	2	1	2		2	3	1		1	2		
12.5		1	1	1					1				
12.0							1	1					
11.0			1	2			1						
10.0		3		1									
Total	1	8	3	9	3	3	5	2	2	4	4	6	3

Over-all total 53 eyes

TABLE 11.—*Correlation of Visual Result with Age of Onset in Infantile Glaucoma*

Age of Onset, Mo.	Visual Acuity												
	6/5	6/6	6/7.5	6/9	6/12	6/15	6/18	6/22	6/30	6/60	6/100	CF	LP
Birth		1	1	2	2	2	1	1	1		3		1
1			1	2			2			2			1
2													
3										1		1	
4		2		2	1					1			1
5												1	
6	1	2	1						1			1	
7						1						1	
8		2											
9		1											
18													
Uncertain				2					1			2	
Total	1	8	3	8	3	3	3	1	2	4	3	6	3

Over-all total 48 Eyes

alone or combined could be used from the start, became blind in both eyes.

Comment

The prognosis for infantile glaucoma has improved greatly as a result of Barkan's work in adapting goniotomy for its treatment. With early operation, blindness from this disease is preventable to a large extent. Early recognition, however, is essential to early treatment. Although the tension can be controlled regardless of the corneal diameter, the further the disease progresses and the more classical the signs the poorer the visual outlook.

Diagnosis is particularly difficult in the approximately two-thirds of patients born with normal eyes but who develop signs of the disease after birth. The first sign to suggest the diagnosis in this group of patients usually is photophobia. Any child under two or three years of age, especially during the first year, who has unexplained photophobia and tearing should be suspected of having infantile glaucoma and the ocular tension recorded under deep anesthesia. Tonometry in this disease offers the same difficulties as in adult glaucoma. Early diagnosis is extremely important in this group of patients to permit early surgery

Fig. 9.—Postoperative photograph showing corneal scarring from pyocyaneous infection of the cornea. Left eye successfully operated. *B*, close-up of right eye.

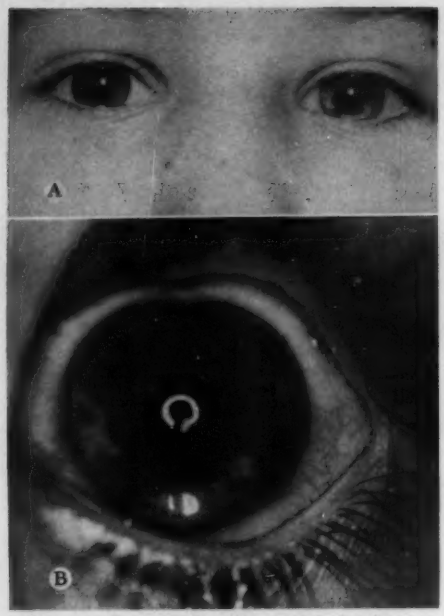

Fig. 10.—Postoperative photograph showing successful control of tension 02, complicated by depigmentation of iris stroma O. S. *B*, close-up of left eye.

before marked enlargement of the eye occurs, which frequently is accompanied by a poor visual result in spite of normalization of tension. Gonioscopy is of little diagnostic help. I believe that I can find nothing characteristic in the angle of the anterior chamber of the eye with infantile glaucoma upon gonioscopic study. The angle is open, and the iris inserts normally as it does in the infant's eye. The scleral spur is almost invariably easily visualized, and the canal of Schlemm fills with blood in a normal position. Attempt was made in 126 eyes to fill the canal of Schlemm with blood by jugular compression or by aspiration of the anterior chamber. Only 10 failed to fill. The diagnosis must be confirmed by tonometry. This offers even greater difficulties than the study of adult glaucoma because of sources of error such as anesthesia which is too light. When question exists, readings must be taken on other occasions.

The two most important etiologic factors in infantile glaucoma seem to be heredity and maternal virus infections. A family history of glaucoma was obtained in 11 patients, and what was thought to be a maternal virus infection early in pregnancy was noted in 7 instances. Congenital anomalies elsewhere in the body, among which cardiac and neurological were commonest, indicated generalized damage to the fetus. An unusual type of renal involvement, which should be investigated further, was found in a small number of children. The entire matter of etiology and the reasons for ocular involvement should be studied more extensively.

The treatment is primarily surgical. Experience with this series of patients indicated that surgery should be carried out as promptly as possible after making the diagnosis. The operations of choice are goniotomy or goniopuncture alone or combined. Either goniotomy or goniopuncture can control the ocular tension when done as a single operative procedure. However, the results in this series seem better when the operations were combined into a single operation, in which a goniopuncture is done upon completion of the goniotomy incision. Goniotomy, when done as a primary procedure on 21 eyes, controlled the ocular tension in 62% of eyes. Goniopuncture done on 44 eyes controlled the tension in 48%, and the combined operation done on 104 eyes controlled the tension in 82%. Over-all results for the entire series of 176 eyes indicated successful control of pressure in 85.8%, including reoperations. With this high percentage of success blindness was unusual, since usually one eye can be salvaged. In the present series of 108 patients only 4 were sightless.

Evaluation of the success or failure of the operation must be based upon the control of tension, as pointed out by Haas,[4] since it is impossible to measure preoperative vision and postoperative vision can be obtained only years later. Furthermore, a poor visual result is frequently due to an advanced stage of the disease previous to surgery.

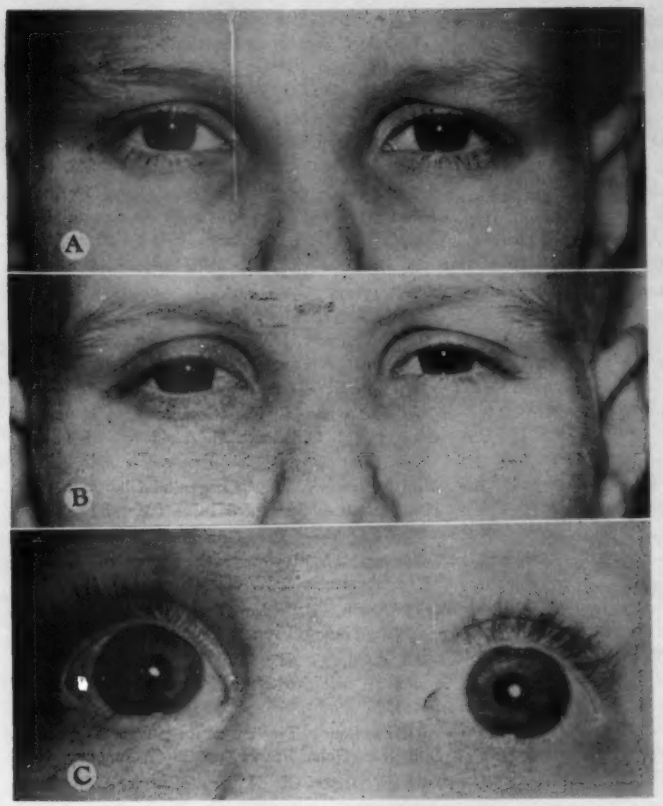

Fig. 11.—Clear corneas in eyes with good visual results. *A* and *B*, identical twins 12 years after surgery.

The results from surgery seem to be permanent. Eyes that have been followed for as long as 12 years are maintaining a normal pressure and retaining vision (Fig. 11). The visual results are excellent if the patient is operated on prior to corneal enlargement and marked ocular damage. The conclusion is made, therefore, that early diagnosis followed by prompt angle surgery is essential. Further investigations regarding the relative merit of goniotomy, goniopuncture, and the combined operation should be done.

Summary

Early diagnosis and early operation are essential in the management of infantile glaucoma.

Photophobia is an important early sign of infantile glaucoma.

The etiology remains somewhat obscure and should be investigated further.

Goniotomy, goniopuncture, or a combination of the two are the operations of choice.

In the present series of patients combined goniotomy and goniopuncture seemed to give the best results.

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The Spectral Sensitivity of Color-Defective Subjects Determined by Electroretinography

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Congenital color defectives, who comprise 8% of the male population,[1] have been studied until recently entirely by psychophysical methods. The object of this paper is to describe the results obtained in the study of color-defective subjects by the method of electroretinography and to compare these results to those obtained by other techniques. These subjects have more than just an interesting novelty but rather an important congenital anomaly, since the severely defective are handicapped in a variety of occupations[2] as well as in the appreciation of their environment.

According to the trichromatic theory of vision there are three color processes.[3] Protanopes and deuteranopes are both referred to as dichromats, since they require only two color primaries to match all other spectral colors. The protanope is considered partially red-blind, since to him the red end of the spectrum appears darkened. According to most investigators, the deuteranope does not show a loss of luminosity in the green and, consequently, his color defect is generally explained as some kind of fusion of the red and green processes.[4,5] Protanomalous and deuteranomalous subjects who are considered as anomalous trichromats make up 1% and 5%, respectively, of the male population, while the less common dichromats comprise only 25% of all color defectives.[2] No attempt will be made here to discuss the complex and varied modifications of numerous color theories.

Since 1952, several electroretinographic studies have been done suggesting a red mechanism between 620 and 630 mμ.[6-9] These investigations usually involved colored adaptation lights or sudden changes in the wavelength of test stimuli designed to "bleach" specific color mechanisms. The only studies involving color-defectives as subjects showed the loss of a red "hump" at 630 mμ in protanopes,[9,10] which was present in deuteranopes and normals. However, maximum sensitivities at 500 mμ[9] suggested the intrusion of scotopic function, and hence the finding of no difference in spectral sensitivity between deuteranopes and normals was not surprising. It is obvious then that a method is necessary, in the study of color processes, which removes the complication of rhodopsin sensitivity as much as possible. Although light adaptation favors the recording of photopic activity, even moderate levels of brightness, as for example 20 foot-lamberts,[8] still allow the intrusion of scotopic processes. Flickering stimuli at a rate faster than 20 per second supply a solution to this problem.[11-14,30]

Dodt introduced the technique used at the National Institutes of Health in a study of two protanopes and two protanomalous subjects, all of whom showed a shift in maximum spectral sensitivity from 558 mμ to 531 mμ among wavelengths available.[12] The protanopes showed a maximum loss of red sensitivity, while protanomals showed a red sensitivity loss intermediate between that of the dichromats and normals. The difference in spectral sensitivity when cor-

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From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare.

rected for equal quantum intensity corresponded favorably to the absorption spectrum of red-sensitive pigment with a maximum at 590 mμ, which Rushton has found to be absent in protanopes.[15] In normal subjects a large stimulus area (60 degrees) was found to give an increased blue sensitivity as compared to small stimulus areas (1 degree). This blue discrepancy was also found in a study of congenital night-blind observers with larger stimulus areas, thus showing a photopic blue sensitivity which suggests a blue-sensitive photopigment with maximum absorption at about 460 mμ.

Because the red color mechanism is lost in protanopes, it was thought the remaining color processes might be further clarified by a study of spectral-sensitivity curves in these subjects with small and large stimulus areas. Four deuteranopes and two deuteranomalous patients were also examined.

Method

To obtain subjects, a notice requesting "color-blind" volunteers was placed in the National Institutes of Health newsletter. About 25 subjects were tested with the Hardy-Rand-Rittler pseudoisochromatic plates, the Farnsworth D-15 Panel, and the Nagel anomaloscope. In general, the anomalous trichromats were able to identify a number of the HRR plates correctly and had little difficulty in correctly arranging the colored discs. The dichromats failed both tests badly. A Nagel anomaloscope proved helpful in the classification of a few doubtful subjects. Most volunteers were young, but in the more elderly subjects the lenses were examined with the biomicroscope

Fig. 1.—A subject is shown in position to be tested. Just in front of the patient's eye is the convex lens for increasing the area of retinal stimulation. The circular wheel contains the double-interference filters, while just to the right of it is a cell containing the neutral density filters. At the far right are the rotating sector disc with the motor shielded by tinfoil, Xenon lamp housing, and JOVY rectifier.

to determine the presence of cataracts or marked yellowish discoloration, which would absorb blue light.

Phenlyephrine (Neo-synephrine), 10% viscous, and proparacaine hydrochloride (Ophthaine), 0.5%, were used for dilation of the pupil and topical anesthesia for the cornea. The patient was seated for the testing procedure with the head steadied by an especially designed frame (Fig. 1). Two ground electrodes were placed on the forehead, with the reference electrode on the bridge of the nose. A Burian-Allen contact lens served as the counter electrode. A 1,000 watt 45 amp. Xenon lamp (Osram) was used as the light source, with the current supplied by a JOVY rectifier. Narrow bands of color with maximum intensity at wavelengths of 404, 419, 442, 456, 473, 502, 523, 531, 558, 583, 610, 626, 648, and 672 mμ were obtained by the interposition of double-interference filters (R-40, GBA Balzers, DAL Schott and Gen.) into the path of the beam. The width of the color bands at half maximum transmission was 15-25 mμ and at 0.001 of maximum transmission was only 60-80 mμ wide. These filters transmit only 1%-2% of the incident light.

Neutral density filters (Inconel filters 31, 34, 38, Bausch & Lomb) were used to alter the stimulus intensity. The neutral density and interference filters were checked spectrophotometrically. A rotating sector disc supplied flicker stimuli of equal light-dark ratio at a rate of 32 per second. The electrical potentials were amplified and recorded on the Grass encephalograph (Model III D, paper speed 6 cm. per second, time constant of 60 msec.). A frequency filter was used to suppress muscle activity which would disturb the record. A heat-absorption glass (KG I, Schott & Gen.) and a heat-reflection filter (Calflex, GBA Balzers) were employed in order to reduce infrared radiation. To determine the energy correction necessary for the differences in radiant energy at each wavelength, a vacuum thermocouple (Type B, Pyrowerk) was used in conjunction with a galvanometer (Leeds & Northrup). The light intensity produced by the Xenon lamp before filtering with either the neutral density or interference filters was 200 lamberts. The subjects were tested in a state of medium light adaptation (13 ft-c. at the eye), while convex lenses of short focal length, with focusing on the cornea, were used to supply areas of retinal illumination subtending angles of 15 or 60 degrees. For small stimulus areas, a parallel beam of light was found to subtend a visual angle of about 1 degree, but because of the high stimulus intensity necessary, an area of about 7 degrees is actually illuminated owing to the scattering effect of the optic media.[12] The data necessary for two spectral sensitivity curves from different size stimulus areas could be recorded in less than 30 minutes.

Results

In the determination of spectral-sensitivity curves, response height is plotted against density of the neutral filters at each wavelength (Fig. 2). The response heights at wavelength 558 mμ were recorded at periodic intervals during the test period so that any significant alterations in amplitude of responses would indicate poor fixation on the part of the subject and invalidate the results. Figure 2 represents the data for a normal subject when a 60 degree stimulus area was used, and, in general, the curves are seen to be sinusoidal, which was characteristic of all the results whether or not the subjects were color defectives. For smaller stimulus areas the slopes were steeper. The spectral-sensitivity curves were determined by finding the density necessary to give a constant response, correcting the density for differences in energy value at different wavelengths, and determining the relative percentages of one density to another for each wavelength. The percentage values are then expressed in log units in plotting the final curve. For each stimulus area a spectral-sensitivity curve was calculated at three criterion values (three response heights—about 25, 50, and 75μv.,

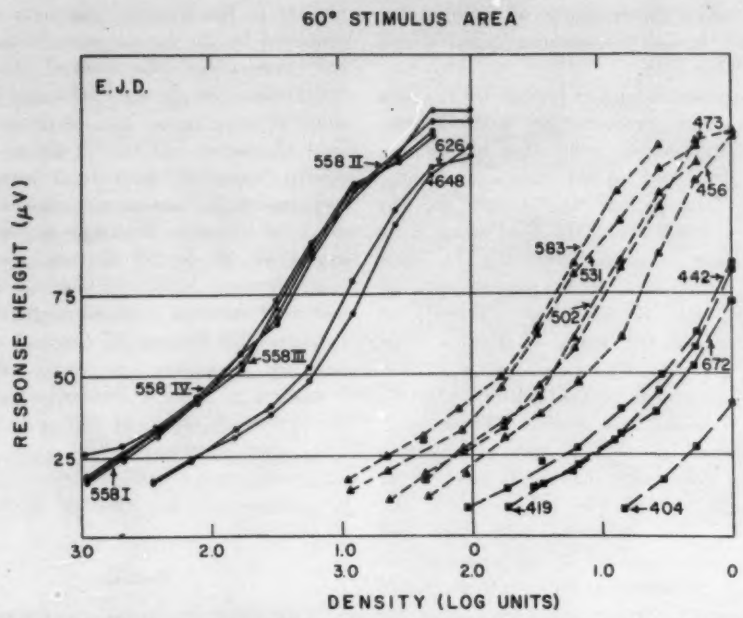

Fig. 2.—Intensity curves for each wavelength at 32 per second flicker are shown for a normal subject with large area retinal stimulation (60 degrees). The relative location of the curves for each wavelength along the horizontal axis has not yet been corrected for energy differences.

except for 404 and 672 mμ, where usually only 25μv. were obtained) and the three curves averaged. This was thought to be justified, since there was little difference in sensitivity regardless of the criterion value chosen. In all subjects there was an increase in blue sensitivity at 456 mμ of about 0.15 log units for the higher criterion value. In the red part of the spectrum there was an at 610 mμ in deuteranopes and normals for increase in sensitivity of about 0.1 log unit the higher criterion value, but in protanopes a loss of sensitivity occurred for brighter stimuli. The increase in blue and red sensitivity at higher criterion values in normals has been described [6] but was less pronounced in this study.

Although it is theoretically desirable to use large stimulus areas and low criterion data (dimmer stimuli) so as to reduce the contribution of indirect stimulation through scatter and reflection,[6,12,17,21] it was found in practice that untrained subjects were less able to tolerate such wide illumination and often allowed their fixation to wander, giving unreliable data. Even the large stimulus area data which could be calculated showed more scatter of results than when smaller stimulus areas were used, as can be seen by comparing the data in Figure 6 to those in Figures 5 or 8. However, as has already been described, the only difference in normals between the spectral-sensitivity curves with small and large stimulus areas is a slight increase in blue sensitivity in the latter. Several additional normals were tested, and again an increase in blue sensitivity was found with large area stimulation (Fig. 3). The difference is not striking, because the curves are based on an average of three criterion values, while it has been shown that the blue "hump" in large area stimulation is accentuated by higher criterion values.[12]

For protanopes it can be seen in Figures 4, 5, and 6 that a loss of red sensitivity is

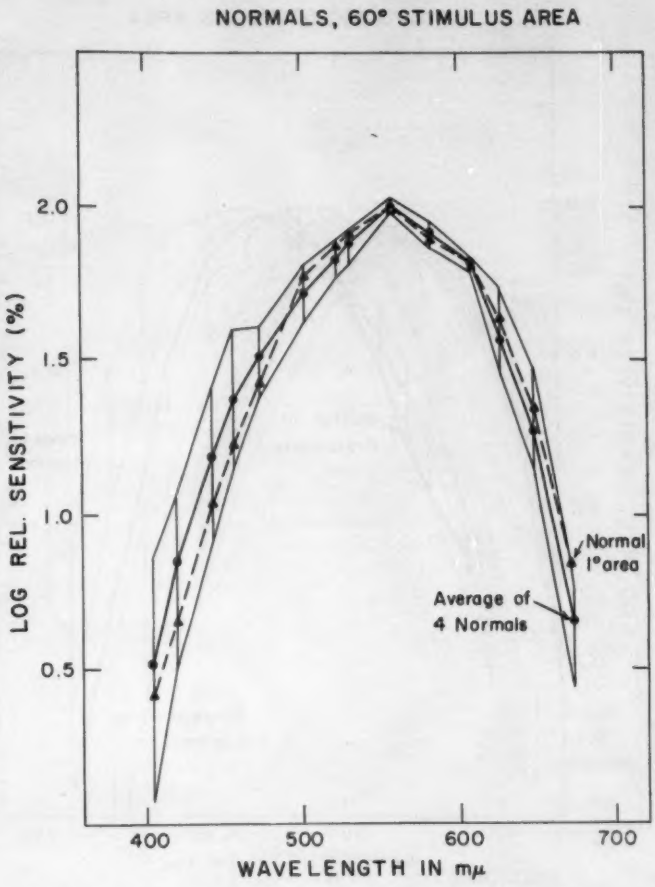

Fig. 3.—The average of four spectral sensitivity curves in normals with a 60 degree stimulus area is shown, with the limits of scatter indicated by the extent of the vertical lines which also indicate the location of wavelengths actually tested. An increase in blue sensitivity is evident for the sensitivity curve obtained with large area retinal stimulation (60 degrees). The broken line represents an average of four spectral sensitivity curves obtained with 1 degree stimulus areas.

evident, regardless of the size of area of retinal illumination. The protanope curve is narrower than the normal, with a shift in maximum sensitivity to about 531 mμ, and the curve appears skewed to the left.

In four deuteranopes the maximum luminosity was shifted to about 583 mμ with a skewing of the curve to the long-wavelength side of the spectrum, with a loss of green sensitivity which extends into the blue. It may be noted that only three deuteranope curves are shown in Figure 8, while the scatter in Figure 5 is dependent on data from four deuteranopes. The great scatter in the blue wavelengths in Figure 5 was due to this fourth deuteranope whose data probably should not have been calculated because of poor fixation at the time of testing. In Figure 8, two deuteranomals who showed matching quotients on the Nagel anomaloscope of 2.7 and 4.0 are shown to have a loss of green sensitivity intermediate between that of deuteranopes and normals. The spectral-sensitivity curves are again skewed toward the longer wavelengths, but in this case the maximum sensitivity is closer to 558 mμ.

The three spectral-sensitivity curves of protanopes found with large stimulus areas (Fig. 6) showed what appeared to be blue "humps" with peaks somewhere between 456 and 473 mμ, which are not obvious in the curves of normals or deuteranopes.

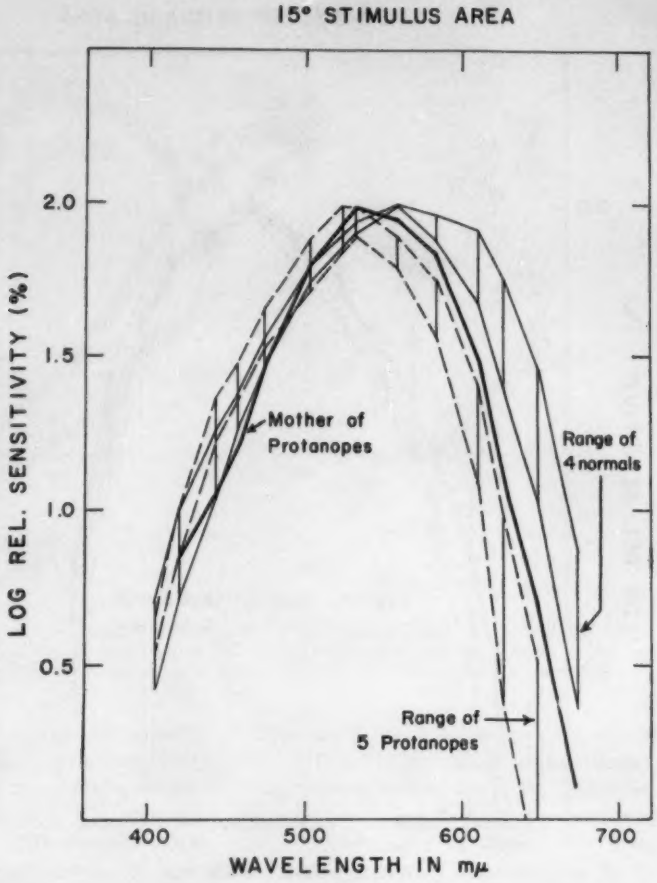

Fig. 4.—The range of spectral sensitivity for four normals and five protanopes is shown with the spectral sensitivity curve of the mother of a protanope.

Comment

It has been traditional to equate the psychophysical luminosity curves of normal and color-defective persons at equal maxima,[4,5] as was done in Figures 5, 6, and 8 in the present study. When this is done, all agree that protanopes show a significant loss in red sensitivity. However, when the deuteranope psychophysical luminosity curves are similarly compared with normals, there is no loss in green sensitivity but only a slight increase in red sensitivity in the region of about 600 mμ.[4] Several studies indicate that the luminosity curves should be lowered in dichromats as compared to normals.[5,18,19] Graham and Hsia [5] found that five out of six deuteranopes show a luminosity loss in the blue-green by measuring flicker-fusion frequency for different wavelengths and by threshold measurements performed at the fovea.

This reported green loss is strikingly similar to that found in this study by electroretinography. One conflicting report has recently appeared suggesting that deuteranopes show a luminosity gain of 36.2% rather than a loss.[19]

In Figures 5 and 8, it can be seen that spectral-sensitivity curves determined by the method of electroretinography show a loss of red sensitivity in protanopes and a loss in green sensitivity for deuteranopes even when the maxima are equated at the same level. Statistically, by the

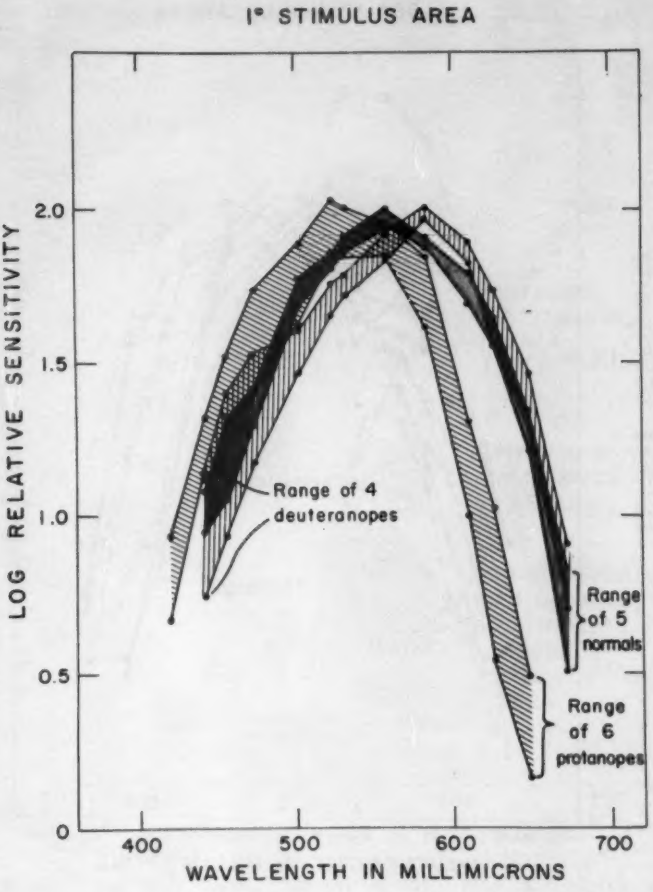

Fig. 5.—The range of spectral sensitivity is shown for four deuteranopes, five normals, and six protanopes.

method of analysis of variance, the groups seen in Figure 5 showed a highly significant difference which was dependent on the shape of the curves and independent of variations in location of their maxima. However, if the sensitivity curves of the dichromats are shifted along the ordinate (Fig. 10), the curves are seen to coincide closely on the red side for deuteranopes and normals and closely on the green side of the spectrum for protanopes and normals. It was found that this arbitrary reduction in sensitivity corresponds excellently to the reduction in sensitivity indicated by the decreased absolute amplitude of responses found in protanopes and deuteranopes as compared to the normal (Fig. 9). The only conclusions that one may draw from these data are that the sensitivity curves in dichromats, determined by electroretinography, should be reduced in comparing them to the normal trichromats. Any attempt to extrapolate the exact reduction in sensitivity from these data is dangerous because of the errors inherent in any method involving intersubject comparisons of response amplitudes by electroretinography. The position of the contact lens [20] and the effect of differences in the amount of retinal pigmentation [21] are examples of factors affecting the amplitude of response among normals.

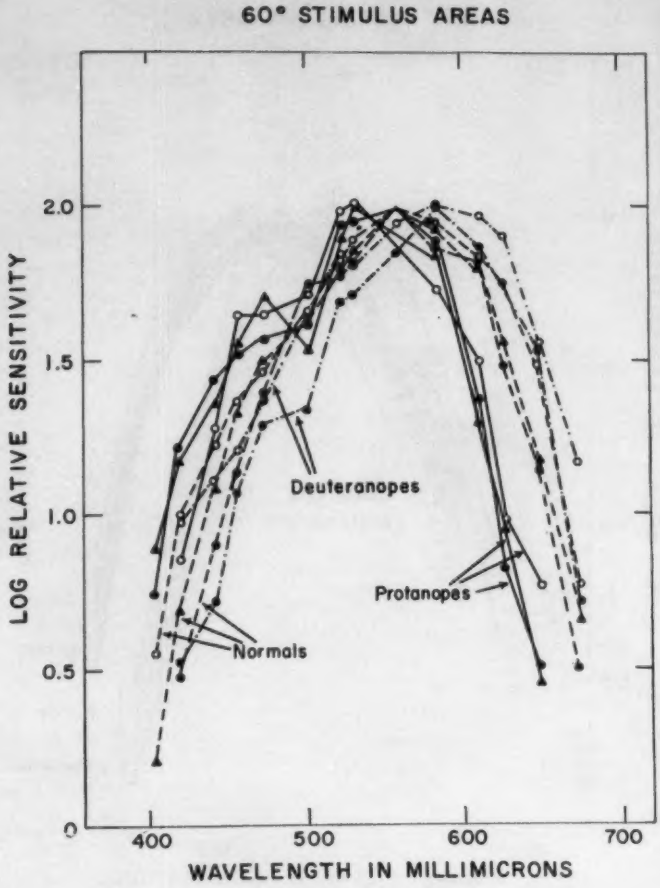

Fig. 6.—Spectral sensitivity curves obtained with large stimulus areas (60 degrees) in two deuteranopes, three normals, and three protanopes.

Recently Rushton [15,16] extended his method for measuring human cone photopigment absorption in situ, which depends on the analysis of light before and after fundus reflection and the differences found after pigment bleaching. Presently this is the only purely physical method for studying color mechanisms in humans and has an advantage over spectral electroretinography in that definite conclusions can be drawn about the photopigments themselves. The interpretation of results obtained by electroretinography is complicated by the alterations of apparent sensitivity produced by pre- and postretinal factors as, for example, lens absorption of blue light and blood reflection of red light.[21,22,31] Also, the exact origin of the electrical potentials recorded remains a mystery, although they are known to be produced somewhere in the region including the bipolar- and photoreceptor-cell layers of the retina.[23-26] Future microelectrode studies will probably supply the answer to this problem.

Knowledge about retinal pigments can be only indirectly inferred by electroretinography, but the method may be important in supplying information about alterations at more proximal retinal levels and contributes data about photopic color processes in the retinal periphery, which bleaching experiments have been unable to do. As

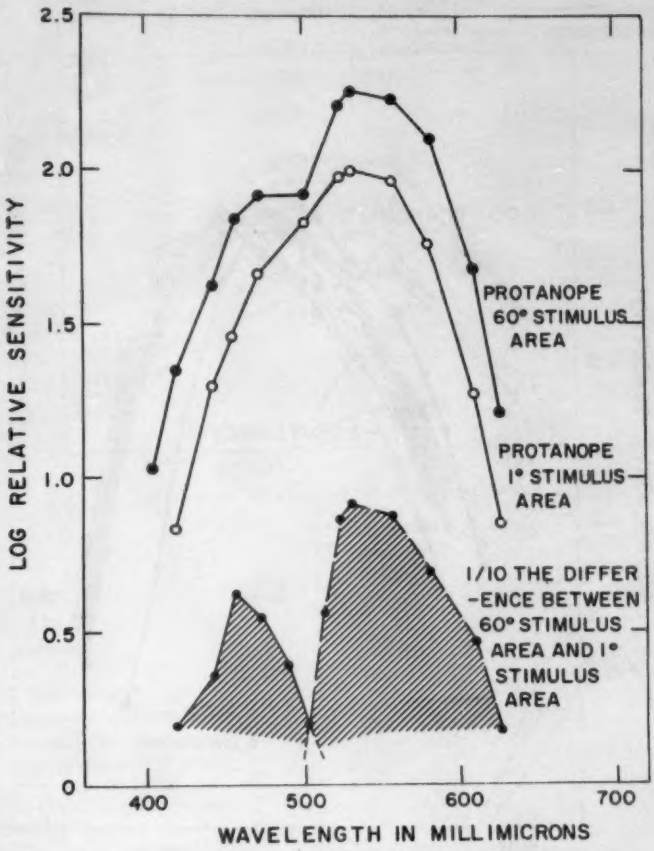

Fig. 7.—The average spectral sensitivity of six protanopes obtained with a 1 degree stimulus area is compared with the average sensitivity of three protanopes with a 60 degree stimulus area. The curves are adjusted according to the differences in density necessary to give a 50μv response at wavelength 558 mμ. The shaded humps below represent the difference between the spectral sensitivity curves shown above (not corrected for equal quantum intensity).

Weale[27] has aptly stated, "the eye is not just a pot full of pigments, but its whole function can be elucidated only by a systematic inquiry into the nervous mechanisms thrown into activity by photochemical action."

Both physical methods have been important in confirming the long-suspected belief that the deficiency in protanopes is at a peripheral locus which is retinal rather than in the optic pathways and that the loss of red sensitivity is in fact due to a loss of red-sensitive pigment.[15]

As was mentioned in the introduction, the maximum difference in spectral sensitivity by electroretinography between the protanope and normal when corrected for equal quantum intensity is at 590 mμ (Fig. 10). This is the peak absorption for the red-sensitive pigment found to be absent in protanopes by Rushton, who has named this pigment erythrolabe.[16] In Figure 10, the difference in sensitivity between the two types of dichromats and the normal is shown, which would suggest that a green-sensitive pigment is present in the normal with a peak absorption between 558 mμ and 531 mμ. It would appear (Fig. 10) that the deuteranope lacks some green-sensitive pigment in the periphery which is present in the normal fovea and has its peak absorption at about 540 mμ, according to Rushton.[16] However, this green-sensitive pigment referred to as chlorolabe was found to be present in deuteranopes by the in situ bleaching method,[16] so that an alter-

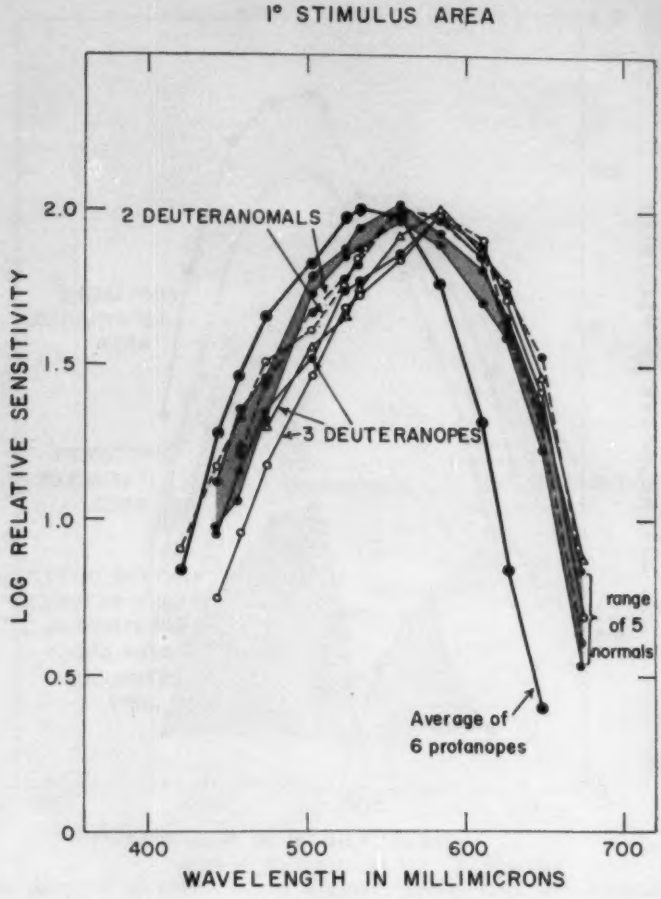

Fig. 8.—Spectral sensitivity curves of three deuteranopes, two deuteranomals, an average curve for six protanopes, and the range of sensitivity of five normals are shown together.

native explanation must be found. In the deuteranope it may be that the green-sensitive pigment is somehow unable to initiate an electrical response when stimulated by light, or perhaps there is an interruption of the electrical paths at higher retinal levels through which the "green impulses" are relayed.

From Figure 8 it may be seen that the loss of green sensitivity in deuteranomals is analogous to the loss of red sensitivity in protanomals, where the loss of sensitivity is found to be intermediate between that of the normal and the dichromat.

When an average of the spectral-sensitivity curves in protanopes with large and small stimulus areas is compared (Fig. 7), by adjusting the sensitivity of the large area curve upward according to the increase in density necessary at 558 mμ to give a 50μv. response in one person, the difference in sensitivity is greatest at about 450 mμ and 530 mμ if corrected for equal quantum intensity. The blue "hump" which is more apparent with large area retinal illumination in protanopes than in either deuteranopes or normals (Fig. 6) would appear to indicate an increased peripheral blue sensitivity in protanopes. This is possibly explained by the replacement of the absent peripheral red-sensitive pigment by blue, just as the "red cones" of the fovea are said to be filled

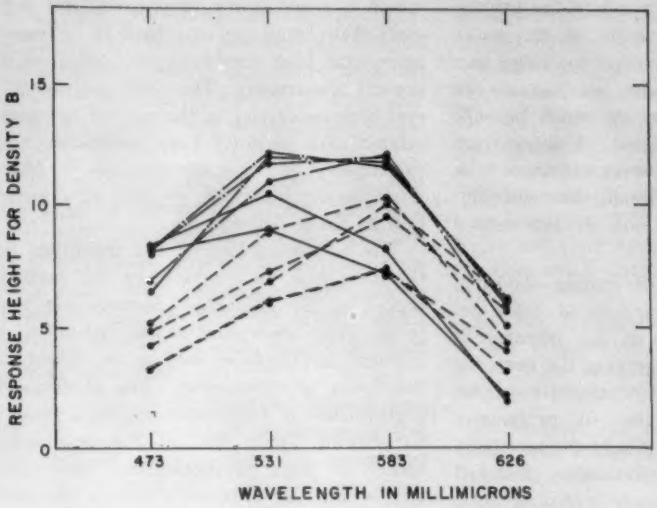

Fig. 9. — Response heights in millimeters (12 mm.=100μv) were found for the four wavelengths shown in four normals (four upper curves), four deuteranopes (dashed lines), and two protanopes (solid lines). (No correction has been made for the differences in energy transmission at different wavelengths.)

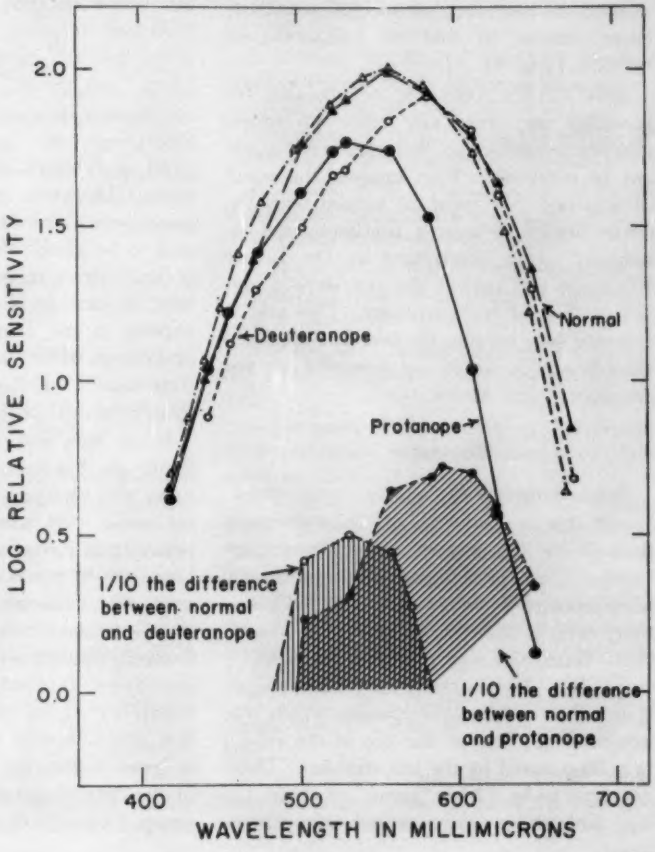

Fig. 10. — The spectral sensitivity curves shown represent an average in each group of the sensitivity curves found with stimulation of a small retinal area (1 degree). The curves are adjusted on the vertical axis according to the differences in absolute density found at wavelength 558 mμ necessary to give a 50μv response. The fourth unlabeled line represents the peripheral (8 degrees from fovea) cone curve found by Wald[29] (psychophysical). The difference curves are shown below as shaded areas (not corrected for equal quantum intensity).

with green-sensitive pigment in the protanope.[16] However, the shape of the sensitivity curve in the protanope for large area stimulation also suggests an increase in peripheral green sensitivity which perhaps may be similarly explained. A comparison between deuteranope curves obtained with small and large area stimuli does not suggest sensitivity alterations in the retinal periphery.

At least one report of finding abnormal luminosity curves in carriers of color deficiency has appeared in the literature.[28] Female heterozygotes carrying the gene for protanopia have shown luminosity curves intermediate between that of protanopes and normals on the red side of the spectrum. A mother of several protanopes, classified as normal according to our screening tests, showed an electroretinal spectral-sensitivity curve similar to that of protanomalous subjects (Fig. 4).

This subject could not be obtained for retesting nor were any other protoform carriers available, so that the result could not be confirmed. Furthermore, the result of this one case must be viewed with extreme caution because a psychophysical luminosity curve, determined by Dr. Louise Sloan, on this patient did not show a significant loss of red sensitivity. This case is reported only because the test data appeared reliable and a significant lowering of red sensitivity was found.

Summary

Spectral-sensitivity curves were determined for a number of color-defective persons by the method of electroretinography. Two protanopes have previously been reported [12] to show a loss in red sensitivity with a shift of the maximum sensitivity from 558 mμ, found in the normal, to 531 mμ. In this study all six protanopes tested showed the same change, which was present regardless of the size of the retinal area illuminated by the test stimulus. There appeared to be a blue "hump" at about 455 mμ with large area retinal stimulation, which is much lower in normals and suggests that protanopes may have an increased peripheral blue sensitivity as compared to normal trichromats. This increased peripheral blue sensitivity in the normal has been related to a photopic blue mechanism and presumably is representative of a blue-sensitive pigment with its peak of absorption at about 450-460 mμ.

The maximum loss of red sensitivity in the protanope, as compared to the normal, occurs at 590 mμ, which corresponds well to the peak absorption of the red-sensitive pigment, erythrolabe, said to be absent in the fovea of protanopes. The absence of erythrolabe in protanopes appears clearly to account for a loss of red sensitivity found in both psychophysical luminosity curves and the sensitivity curves obtained by electroretinography.

A loss of green sensitivity was evident in the spectral-sensitivity curves of deuteranopes, and the maximum loss appears to correspond reasonably closely to the peak absorption of green-sensitive pigment (540 mμ) which is present in the human fovea. However, this green-sensitive pigment, which has been called chlorolabe, is said to be present in the fovea of deuteranopes.[16] It is suggested that either chlorolabe is unable to initiate an electrical impulse in the deuteranope when bleached or perhaps there is an interruption in the transmission of these "green impulses" at more proximal retinal levels.

It has been traditional to equate the maximum sensitivities of normal and deuteranope psychophysical luminosity curves at the same level which gives them the appearance of having equal green sensitivities. Some recent psychophysical and electroretinographic evidence is cited that indicates the deuteranope sensitivity curve should be lowered, thus showing a reduction in green sensitivity. It should be noted that spectral-sensitivity curves of three deuteranopes in this study showed a highly significant loss in green sensitivity, even when the maxima of the normal and deuteranope curves were equated equally in the traditional manner.

In fact, by determining the relative amplitudes of responses for several selected wavelengths, it would be possible in a test period as short as 10 minutes to determine whether a subject was deuteranopic, protanopic, or normal.

The spectral-sensitivity curves of deuteranopes by electroretinography showed a maximum sensitivity at 583 mμ and appeared narrower than the sensitivity curves of normals. Two deuteranomalous subjects showed a loss of green sensitivity which was intermediate between that of normals and deuteranopes.

The results in deuteranopes indicate that the site of the defect in deuteranopia and probably in deuteranomaly is peripheral (not in the optic pathways) and lies somewhere in the region including the photoreceptor-cell and bipolar-cell retinal layers.

This study was made possible through the guidance and instruction supplied by Dr. Eberhard Dodt. The assistance of Dr. Peter Gouras in the calculation of some of the data is greatly appreciated.

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The Penetration of C^{14}-Labeled Atropine into the Eye

A Comparison of Methods of Application

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Although atropine is one of the oldest drugs known to man and has been widely used as a mydriatic agent, information concerning its penetration into the eye has been gauged, more or less, by the onset of its cycloplegic action and gross effects on the pupil. Two common methods for introducing atropine into the eye are by topical application to the cornea and conjunctiva and by subconjunctival injections.

The passage of drugs through the cornea into the globe is generally considered to be a process of simple diffusion.[1] However, since there is a difference in the penetration of chemical compounds with polar and nonpolar constituents there may be an active transport of drugs through the cornea.[2] In this transport the pH of the solution seems to be an important factor.[3] Identification of chemical compounds after their ingression into the eye has been made in a few instances. Recently Hamashige and Potts [4] traced the penetration of C^{14}-labeled cortisone through the cornea and studied its distribution in the cornea, aqueous humor, and uvea. Furthermore, the passage of procaine into the cornea, iris, and aqueous after subconjunctival injection has been studied by Schlegel and Swan.[5]

The present study was undertaken in order to study the penetration into the eye of C^{14}-labeled atropine when it was administered by the subconjunctival route. In addition, a comparison has been made of subconjunctivally administered atropine with the penetration of atropine when it was applied topically onto the cornea and conjunctiva.

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Methods

Albino rabbits, weighing 2-3 kg., were anesthetized lightly with pentobarbital sodium, and tetracaine (Pontocaine) was applied topically to the eyes before the atropine was given. Atropine was administered either subconjunctivally, presumably outside of Tenon's capsule, or topically to the eye and was labeled on the tropic acid moiety ($C_6H_5C^{14}H(-CH_2OH)-COOH$) and made up as a 1% atropine sulfate solution; 0.25 ml. of this solution, which contained 0.48μc., was administered to each eye studied. Before enucleation the rabbits were placed under deep pentobarbital sodium anesthesia.

The atropinized eyes were studied at specific time intervals. Before the eyes were removed, the cornea was washed thoroughly and aqueous humor was withdrawn through an anterior chamber puncture. After enucleation, the eyes were opened near the equator and the lens and vitreous humor were removed. The iris and ciliary body, choroid and sclera, cornea, and retina were separated, washed carefully, blotted, and weighed. The conjunctiva and lens were not saved. It was not possible to retain in the conjunctiva all of the radioactive material that had been injected subconjunctivally. Furthermore, homogenized lens material when plated made a layer on the planchet which was too thick for counting.

The aqueous humor was divided into two portions, each of which was diluted up to 1 ml. with water. Part of one portion was plated directly on stainless steel planchets, while the other was deproteinized with $Ba(OH)_2$ and $ZnSO_4$ before it was plated. One-fourth of the vitreous humor was plated without being diluted. Blood plasma or urine, 0.5 ml., was plated directly on planchets. The total volume of plasma was calculated on the basis of 51 ml. per kilogram of body weight, and a specific gravity of 1.025 was used for calculating the total weight of the plasma.

The solid tissues were homogenized in 50% ethanol and centrifuged. Aliquots of the supernatant fluid were plated. The planchets were dried at room temperature and then placed in a vacuum desiccator overnight. The radioactivity of two samples from each tissue was measured in an internal flow counter (Tracerlab Model SC-50) which was calibrated with Nuclear Chicago Standard $BaC^{14}O_3$. The values were corrected for self-absorption. The probable error of the C^{14} count was 1%-2% for tissues with high C^{14} concentrations and 2%-3% for those with low concentrations. The values recorded in the tables and graphs represent the results of at least two eyes; usually not more than three eyes were studied because of the limited amount of labeled atropine that was available.

In the study on freshly killed rabbits, the animals were anesthetized with ether until respiratory movements stopped. Then the thoracic cavity was opened and the aorta tied off. The atropine was immediately injected subconjunctivally. In the experiments in which atropine was instilled topically, the rabbit head was placed on its side and the eyelids were elevated. This procedure made certain that the atropine covered the cornea as well as the conjunctiva.

Urine was taken by aspiration of the bladder after enucleation. Ordinarily the rabbits did not urinate during the first five hours of the study.

In a few instances, one-dimensional paper chromatograms were run according to the

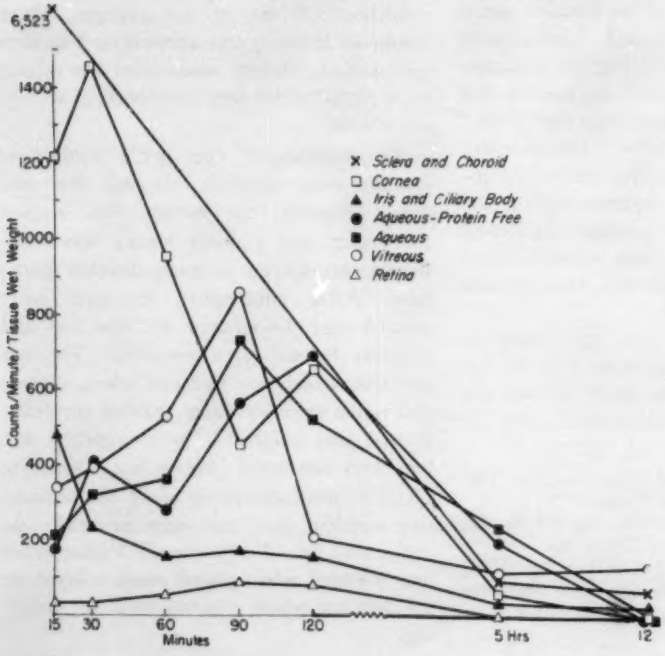

Fig. 1.—Distribution in living rabbits of C^{14}-labeled atropine injected subconjunctivally.

method of Gosselin et al.[6] in order to find out, if possible, what radioactive compounds were present in the various tissues. In addition, radioautograms were made of these paper strips. The radioactivity, when sufficient to be measured, gave *Rf* values similar to those obtained from a known sample of atropine or tropic acid. No effort was made to separate these compounds.

A. Subconjunctival Administration.—1. Living Rabbits: Atropine entered the eye readily after subconjunctival administration. Within 15 minutes the greatest amount of the drug was found in the sclera and choroid, but a considerable amount was also present in the cornea (Fig. 1). The aqueous and vitreous humor and the iris and ciliary body showed some radioactivity at this time, but only a trace was found in the retina. In 30 minutes the cornea showed some increase in activity as did the aqueous and vitreous humor, but the iris and ciliary body showed some decline. The highest levels of radioactivity were found in the aqueous and vitreous humor between one and two hours; at five hours all the tissues showed a marked decline in radioactivity. It is of interest, however, that at five hours the radioactivity of the aqueous was higher than that of any other part of the eye, while no radioactivity was found in the retina. At 12 hours most of the radioactivity had left the eye, although small amounts were still present in the vitreous, sclera and choroid, and iris and ciliary body.

The question arose as to what happened to the injected atropine once it disappeared from the eye. To check this point, the C^{14} activity of the blood plasma and urine were determined in certain instances. Radioactivity began to appear in the blood shortly after atropine had been injected subconjunctivally and subsequently appeared in the urine. Table 1 shows some determinations of the radioactivity of the plasma as well as some determinations for the urine. It will be noted that plasma levels of radioactivity were the highest in 30 minutes after the injection and decreased thereafter, and so at 12 hours no activity was present. It is interesting to note, also, that at five hours 94% of the radioactivity was present in the urine. No attempt was made to collect voided urine, and this may account for the low radioactivity of the urine at 12 hours. Also, no attempt has been made in this study to determine the nature of the compound or compounds which have radioactivity in the urine, but presumably some was atropine and the rest metabolic products of atropine.[7]

Only a relatively small amount of the subconjunctivally injected material was found in the ocular tissues. For instance, in 15 minutes radioactivity corresponding to only 0.49% of the total amount of administered atropine was found in the sclera and choroid. The rest of the eye tissues, with the exception of the lens and conjunctiva, contained only 0.77%. It will be noted in Table 1 that the activity for the

TABLE 1.—*Per Cent of C^{14} Activity Recovered*

Tissue	15 Min.	30 Min.	1 Hr.	1½ Hr.	2 Hr.	5 Hr.	12 Hr.
Live Animals (Subconjunctival Injection)							
Sclera & choroid	1.49	--	--	--	--	0.03	0.02
Rest of eye	0.77	0.65	0.53	0.55	0.52	0.14	0.04
Plasma	--	6.81	6.33	4.82	2.59	4.33	0.00
Urine	--	--		--	--	94.19	5.07
Freshly Killed Animals (Subconjunctival Injection)							
Sclera & choroid	5.08	6.17	4.48	4.23	--	--	--
Rest of eye	2.55	2.49	3.08	2.19	--	--	--
Topical Instillation							
Sclera & choroid	--	0.38	--	--	--	--	--
Rest of eye	--	2.52	--	--	--	--	--

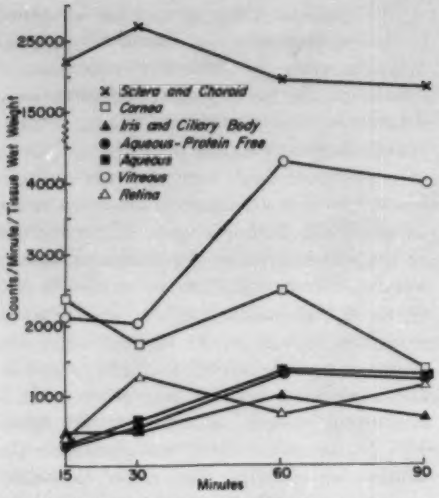

Fig. 2.—Distribution in freshly killed rabbits of C^{14}-labeled atropine injected subconjunctivally.

eye declined during the next 12 hours. In fact, at the time the animals were killed at 12 hours, there was only 0.02% in the sclera and choroid and only 0.04% remaining in the rest of the eye.

2. Freshly Killed Rabbits: These animals received atropine having the same amount of radioactivity as that which was given to the living rabbits. It was interesting to note that after 15 minutes the vitreous body had approximately seven times the amount of radioactivity that was found in the living animal (Fig. 2). Greater amounts of C^{14} were also found in the retina, sclera and choroid, and cornea, but the levels in the iris and ciliary body were similar to those of the living rabbits. The radioactivity of the samples collected at 30 minutes was greater than samples collected at 15 minutes. This increase was much more apparent in 60 minutes. For instance, the retina at this time had approximately 13 times the radioactivity of what was found in the living animal at a corresponding period of time. Likewise, it was eight times that of the living animal in the vitreous humor, three times in the cornea, four times in the aqueous, while it was sixfold in the iris and ciliary body. After one and one-half hours, the longest period in which the freshly killed animals were studied, there was no great change in this relationship between the ocular radioactivity of these two groups of animals. The total amount of C^{14} found in the ocular tissues at various periods of time was also higher than that found in the living rabbit (Table 1).

B. Topical Instillation.—The topical application of atropine to the eye had the advantage of being absorbed through the cornea as well as the conjunctiva. Consequently, higher levels of radioactivity were found in the eye after this method of application. The total amount of radioactivity found in various parts of the eye 30 minutes after the topical instillation of atropine is shown in Table 2. The aqueous humor

TABLE 2.—*Distribution of C^{14}-Labeled Atropine Thirty Minutes After Topical Instillation*

Tissue	Counts/ Min. Wet Weight	% Recovery of Applied Counts	% Above Subconjunctival Injection in Living Rabbits
Protein-free aqueous humor	5,843	--	--
Aqueous humor	6,189	1.41	1,666
Vitreous humor	1,320	0.30	340
Cornea	3,091	0.70	213
Iris & ciliary body	439	0.10	188
Conjunctiva & nictitating membrane	3,695	0.84	--
Sclera & choroid	1,653	0.38	--
Retina	57	0.01	180
Eyelids	532	0.12	--
Unabsorbed atropine	294,583	66.92	--
Total	317,402		

showed the highest levels, in fact, over 16 times that found in the living animals injected subconjunctivally. Part of this increase was caused, perhaps, by the incomplete washing of atropine from the surface of the cornea despite the precautionary measures taken. Likewise, the vitreous humor, cornea, iris, and ciliary body had atropine levels two to three times those found in rabbits given subconjunctival injections. Furthermore, at 30 minutes the total amount of atropine in the eye, with the

exception of the sclera, choroid, lens, and conjunctiva, was higher for the animals receiving topical atropine (Table 2). The sclera and choroid, in this instance, had less atropine, probably because this material was not placed adjacent to these structures as was the case when it was given subconjunctivally.

An attempt was made to recover the unabsorbed atropine when it was applied topically. Approximately 67% of the atropine was found in the washings from the cornea and conjunctiva. Moreover, approximately 2.5% was found in the eye tissues (Table 2), and the remainder was presumably in the blood plasma and urine, although the latter fluids were not tested for radioactivity in this phase of the study.

Comment

The pathway taken by subconjunctivally injected atropine into the eye proper is not clear. It is easy to assume that it is picked up by the blood vessels going to the ciliary body and iris, where it is distributed to the different parts of the eye. However, in order to do this it must be picked up by capillaries in the area adjacent to the injected material, but these capillaries would be draining into venules and veins leaving the eye rather than entering the eye. Likewise, if it were picked up by the lymphatic vessels it would be draining away from the eye. Although details of the circulation of the rabbit's eye has not been worked out, presumably it is quite similar to that of the rat [8] or the human being.[9] In the eyes of these species, capillaries in the conjunctiva drain either into conjunctival veins or into veins in the limbus, which may drain through the sclera on their way back to the ophthalmic veins. Such pathways do not explain how the atropine gets into the structures associated with the anterior chamber of the eye.

The question thus arises as to whether atropine or other materials that enter the eye after subconjunctival injections enter by simple diffusion or by active transport across the various membranes. This question was tested in freshly killed rabbits in which the aorta was tied off. Atropine was injected subconjunctivally into these animals and went into the eye readily; in fact, in one and one-half hours more had accumulated in the eye than in eyes of living rabbits treated for the same period of time. It appeared, therefore, that the atropine probably entered the eye by simple diffusion and that the higher concentrations were present because the circulatory system was not picking up the material.

Of course, when the circulation stops, various membranes lose their semipermeability.[10,11] This would permit easier diffusion of atropine. It is not possible to tell exactly what pathway is being used by the atropine in entering the eye. However, since it appears in the sclera and choroid, retina, and vitreous within a few minutes after it is injected, presumably it is diffusing through these membranes. Moreover, atropine is found in relatively high concentrations in the cornea within 15 minutes after it is given. Probably this is accomplished by a direct transfer along the connective tissue of the sclera and conjunctiva into the substantia propria of the cornea. Contamination of the cornea from the subconjunctivally injected atropine cannot be ruled out because of the close proximity of these structures.

Moreover, it is not necessary to assume that atropine is secreted into the posterior chamber of the eye by the ciliary body, because it entered the aqueous in the freshly killed animal just as readily as in the living rabbit. Consequently, the atropine probably diffuses into the aqueous through the cornea as well as through the iris and ciliary body.

Presumably, the radioactive material in the eye is atropine. It is true that much of the atropine can be metabolized to tropic acid and tropine by the time it is excreted.[7] However, since these metabolic products do not produce mydriasis, it is thought that at least some of the radioactive material found in the eye after it is applied to this organ is atropine per se.

There was some indication in a preliminary study that atropine might be bound to the protein in the aqueous humor. Because of this the radioactivity of the aqueous was determined in protein-free filtrates as well as in the aqueous proper. The assumption that the atropine was bound to the protein was apparently not correct because the concentrations of this material found by the two methods were very similar.

Summary

The penetration of C^{14}-labeled atropine into the eye when given subconjunctivally to living and freshly killed rabbits, as well as when applied topically to the cornea and subconjunctiva of living rabbits, has been studied.

It is apparent that atropine enters the eye by diffusion and that a functioning circulatory system is not a prerequisite for this penetration. The C^{14}-labeled material is found in all parts of the eye, even in the retina.

More atropine enters the eye after topical instillations, provided the cornea is covered with the material, than when similar amounts are given subconjunctivally.

Most of the C^{14}-labeled material is present in the urine within five hours after it has been given subconjunctivally.

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Clinical Comparison of the Berens-Tolman Ocular Hypertension Indicator with the Schiötz Tonometer

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In recent years, surveys have indicated that approximately 2% of persons over 40 years of age have undiagnosed glaucoma.[1-3] In order to detect chronic simple glaucoma in its early symptomless stage, it seems desirable that in patients over 40 tensions should be taken routinely during general physical examinations. With this in mind, the Berens-Tolman Ocular Hypertension Indicator was introduced[4] to the medical profession in 1950 and was later modified somewhat as described in a statistical report of its use by Cholst and Horovitz.[5] In the latter paper, the Berens-Tolman and Schiøtz instruments were compared on 180 glaucoma patients (number of eyes not stated), with use of a 5.5 gm. weight on the Schiøtz tonometer and the 1948 Schiøtz calibration scale. Of 57 eyes with tensions elevated to between 30 and 60 mm. Hg, 54 (95%) registered "high" on the OHI and 3 (5%) registered "normal" (false negatives). In 35 eyes with tensions below 15 mg. Hg, the Berens-Tolman Indicator recorded "low." The remaining eyes (number not noted) registered between 19 and 28 mm. Hg, with "normal" reading on the OHI. In a control series of 32 nonglaucomatous eyes, they found normal tensions both with the Schiøtz instrument and the OHI.

Recently, a similar comparison was made in the Glaucoma Clinic of the Illinois Eye and Ear Infirmary with 1,000 tension determinations on 524 patients with various types of glaucoma (Table 1). All tensions were performed by me after approximately 20 months' experience in the Glaucoma Clinic. Approximately one-fourth of the Schiøtz determinations were done with a 7.5 gm. weight and the remainder with a 5.5 gm. weight on the tonometer. In each instance, the Schiøtz determination was immediately preceded or followed by an OHI determination. On alternate days alternate instruments were used first. Where a discrepancy appeared between the findings of the two instruments, the readings were rechecked.

As measured on the Tolman Micrometer, the OHI "normal" reading corresponds to 3.6 on the Schiøtz scale. Berens stated[3] that with practice discrimination on the OHI should not exceed ±1 Schiøtz scale

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TABLE 1.—*Comparison of the Berens-Tolman Ocular Hypertension Indicator and the Schiøtz Tonometer in One Thousand Eyes*

			OHI		
Schiøtz, Mm. Hg	OHI	No. Eyes	Corresponds to Schiøtz	Lower Than Schiøtz	Higher Than Schiøtz
More than 27	"High"	225	141 (62.6%)	84 (37.4%) "False negatives"	0
19-27	"Normal"	530	400 (75.3%)	95 (17.9%)	26 (6.8%) "False positives"
Less than 19	"Low"	245	160 (65.3%)	0	85 (34.7%)

unit. Taking 3.6 as the exact "normal," the expected range of normal readings would therefore fall between 2.6 and 4.6 on the Schiøtz scale. This range corresponds to tensions of 19 to 27 mm. Hg on the 1955 Schiøtz calibration scale with the 5.5 gm. weight. Accordingly, this range was selected as normal in this comparison series. In other words, all eyes registering between 19 and 27 mm. Hg on the Schiøtz tonometer should have indicated "normal" tension on the OHI. Those registering above 27 mm. Hg Schiøtz should have indicated "high" on the OHI, and those registering below 19 mm. Hg Schiøtz should have indicated "low" on the OHI.

Reference to Table 1 will show that out of 1,000 determinations, 225 eyes registered higher than 27 mm. Hg Schiøtz. Of these 225, 141 (62.6%) showed a good correlation and registered "high" on the OHI. The remaining 84 (37.4%) registered "normal" on the OHI, whereas they should have indicated "high." Of these 84 apparently false negatives on the OHI, 10 registered 28 mm. Hg Schiøtz, 40 registered 29 mm. Hg Schiøtz, 24 registered 30 mm. Hg Schiøtz, and 10 registered higher than 30 mm. Hg Schiøtz. It is evident therefore that the greatest number of false negatives occurred in the range of 28 to 30 mm. Hg Schiøtz. Of the 84 false negatives, 74 (88%) lay in this range. Of those 530 tensions ranging from 19 to 27 mm. Hg Schiøtz, the OHI verified 409 (75.3%) as "normal," indicated 95 (17.9%) as "low" and 26 (6.8%) as "high." The latter figure may represent false positives by the OHI or false negatives by the Schiøtz. There were 245 tensions below 19 mm. Hg Schiøtz; the OHI verified 160 (65.3%) of these as low and indicated 85 (34.7%) as normal.

A study of these figures shows us that 26 false positives in a series of 1,000 tension determinations would result in a false referral rate of 2.6%. This may be considered as insignificant. An OHI reading of normal when it should read low is certainly of no significance. The 37% of apparently false negatives might give cause for concern, and it was felt that a readjustment of the OHI might reduce this percentage. To test this opinion, an OHI was reset to read normal at a setting of 4.5 on the Tolman and on the standard Comberg micrometers. This setting corresponds to 18.9 mm. Hg with a 5.5 gm. weight on the 1955 Schiøtz scale. The OHI readjusted to this setting permits easy recognition of a "high" reading when tested on a micrometer set at 2.5 (26.6 mm. Hg Schiøtz). There is therefore a new correlation between the OHI and the Schiøtz readings—the OHI now being adjusted to read "high" within the upper limits of the previously selected range of normal. The following data will prove that this altered relationship is desirable and serves to increase the value of the OHI as a screening device.

Starting on March 30, 1959, a fresh series of tension comparisons was run on 192 glaucoma patients, with a total of 369 tension determinations. A 5.5 gm. weight was used on the Schiøtz tonometer, and the operational details of the series were identical to those described in the first series. Table 2 has been set up identical to the plan of Table 1, with the exception that the OHI readings are based upon the instrument readjusted as described above. A breakdown of the figures shows that the OHI now produces only 4.2% of apparent false negatives and 11.3% of apparent false positives. Surprisingly, the percentage of hypotensive eyes registering "normal" on the OHI is now 58.7%. Although I am unable to explain this discrepancy, I feel that it is of no clinical significance, since the instrument is only meant to be a hypertension indicator. The 11.3% of apparent false positives, with three exceptions, registered tensions of above 23 mm. Hg. Therefore, although they are classified as false positives by the arbitrary scale in this paper, they probably should be considered glaucoma suspects by the latest concept of what constitutes normal tension.[6,7]

TABLE 2.—*Comparison of the Readjusted Beren-Tolman Ocular Hypertension and the Schiøtz Tonometer in Three Hundred Sixty-Nine Eyes*

			OHI		
Schiøtz, Mm. Hg	OHI	No. Eyes	Corresponds to Schiøtz	Lower Than Schiøtz	Higher Than Schiøtz
More than 27	"High"	95	91 (95.8%)	4 (4.2%) "False negatives"	0
19-27	"Normal"	194	166 (85.5%)	5 (3.2%)	23 (11.3%) "False positives"
Less than 19	"Low"	80	33 (41.3%)	0	47 (58.7%)

Comment

The OHI has the advantages of small size, durability, ease of plunger action with little tendency for sticking, and relatively small cost. The small size and durable construction permit it readily to be carried in the physician's bag or pocket. It can be cleaned with water, but plastic solvents, such as ether, should not be used on it, as they tend to dissolve the cement which holds the scale-reading lens in position.

The disadvantages center around the scale indicator which gives slightly over $\times 2$ optical magnification, as compared to the $\times 20$ mechanical magnification of the Schiøtz tonometer scale. Since the OHI scale must be read from above, the instrument must be adjusted to the patient's eye largely by the sense of touch. This requires practice. The scale can be read from the side, but the examiner's eye must be on a level with this portion of the scale in order to read it accurately—to reach this position, he must sit on or near the floor. Relative to experience with the Schiøtz tonometer, Zeller and Christensen[2] have shown that interns can use this instrument to detect early glaucoma. They quote a series of 1,000 tension determinations in which there were no false negatives.

Conclusions

Comparing the Berens-Tolman Ocular Hypertension Indicator and the standard Schiøtz tonometer in a series of 1,000 tension determinations, there was an apparent false-negative rate of 37% when the OHI was set at 3.6 on the micrometer. This rate would have been much higher had we considered 22 mm. Hg as the upper limit of normal instead of 27 mm. Hg. However, with the instrument readjusted to read normal at 0.225 mm. corneal indentation (4.5 on the micrometer), the false-negative rate was reduced to 4.2% in a series of 369 tensions.

These data suggest that the OHI when suitably adjusted can be accurate in detecting early intraocular hypertension and that it should be a useful tool in the physician's armamentarium.

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Turnover of Total Carbon Dioxide in the Aqueous Humors and the Effect Thereon of Acetazolamide

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The rate of turnover of free carbon dioxide and bicarbonate ion (total carbon dioxide) in the anterior chamber of the eye of the rabbit has been estimated to be about 4% per minute.[1] The separate rates of turnover of the several components of the bicarbonate system were taken into account in making the calculation, but no allowance was made for the possible accelerating effect on the turnover due to the conversion of carbon dioxide to bicarbonate ion. Moreover, the calculated value for the rate also depended upon the validity of the assumption that the difference in the pH between the aqueous humor and plasma before and after giving acetazolamide (Diamox) remained constant, that the drug had no effect on the rate of diffusion of either carbon dioxide or bicarbonate ion, and that the flow rate of aqueous humor was reduced to one-half by the acetazolamide. Since these assumptions may not be exact, the value for the turnover rate must be regarded as an approximation.

Unfortunately, the method employed for estimating the turnover in the anterior chamber was not applicable for the estimation of the turnover in the posterior chamber, but preliminary experiments employing bicarbonate labeled with C^{14} did indicate that the rate was very rapid compared with other substances.

It was thought that a more detailed study of the turnover of total CO_2 would lead to greater insight into some of the fundamental processes involved in the production of aqueous humor as a whole and possibly also to a better understanding of how the intraocular pressure is maintained and controlled. Furthermore, it is known that acetazolamide and related compounds affect one of the parameters of the system of aqueous humor dynamics, a consequence of which is the lowering of intraocular pressure and a reduction in the concentration of the total CO_2 in the aqueous humors. Accordingly it seemed worth while to investigate the turnover of total CO_2 not only in normal animals but also in those given this drug.

Methods

All of the experiments were performed on rabbits which were wrapped in towels to prevent struggling. Freshly prepared acetazolamide (50 mg. per kilogram) and 20μc. of radioactive bicarbonate, as sodium salts, were administered intravenously. Samples of aqueous humor were obtained from the posterior chamber and immediately thereafter from the anterior chamber with use of calibrated micropipettes and techniques previously described.[2] The eyes were anesthetized topically with tetracaine hydrochloride and were tapped but once. Three blood samples were obtained from each animal by heart puncture and centrifuged under paraffin oil.

Radioactivity of the samples was assayed by delivering known volumes of plasma and aqueous humor into 50μl. of 2% solution of $Ba(OH)_2$ on flat copper planchets. The samples were spread on the planchets with a small glass rod and dried in air. The value for self-absorption was determined in

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preliminary studies using comparable volumes of aqueous humor and plasma. A positive correction of 6% was found and applied for the anterior aqueous humor and 16% for the plasma. The radioactivity of the samples was counted with a shielded end-window counter (Tracerlab TGC-2) and a decade scaler. All planchets were counted for a time sufficiently long to limit the standard error to less than 5%. Radioactivity counts were corrected for background, but no correction was made for loss by coincidence because of the low rate of counting.

The radioactivity per unit weight of plasma water at two minutes after the injection of C^{14} bicarbonate was arbitrarily assigned a value of 100. The radioactivity in the same quantity of aqueous humor is expressed on the same scale.

Results

The concentration of C^{14} in the aqueous humors of the posterior and anterior chambers relative to that in the plasma at various periods after giving C^{14}-labeled bicarbonate is shown for normal rabbits in Figure 1. The points represent sliding averages by fives. The Figure shows that the total labeled carbon dioxide entered the posterior chamber extremely rapidly. Actually the sliding averages tend to shift the points slightly to the right, and so the rate of accumulation is still greater than the data would indicate. In one experiment in which a sample of plasma and one of aqueous from the posterior chamber were obtained within 45 seconds after injection of bicarbonate the radioactivity per unit volume in the latter fluid had already exceeded that in the plasma. While the rate of accumulation is too great to permit a quantitative evaluation of the $t_{1/2}$, or half-turnover time, it must be less than about 10 seconds.

The rate of accumulation of total labeled CO_2 in the anterior chamber is much lower than in the posterior chamber, but the transfer is relatively rapid as compared with such other constituents of the aqueous as sodium or chloride.[3]

The accumulation of total CO_2 in the aqueous humor of the posterior and anterior chambers was determined in rabbits given an intravenous injection of 50 mg. of acetazolamide per kilogram 15 minutes prior to the administration of radioactive bicarbonate (Fig. 2).

The relatively short time interval after injection was selected for these experiments for two reasons: Wistrand[4] found that approximately half of the acetazolamide disappeared from the rabbit plasma within 20 to 25 minutes, and Langham and Lee[5] reported that the rate of flow of aqueous

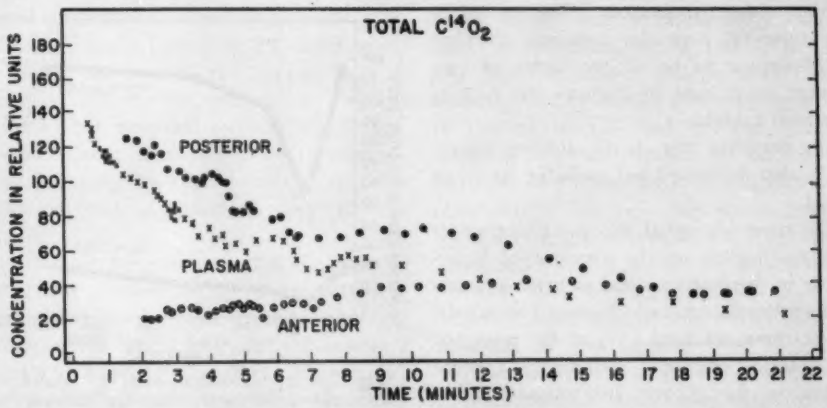

Fig. 1.—The concentration of C^{14}-labeled total carbon dioxide in the plasma, posterior and anterior chambers in the eyes of rabbits at various intervals after intravenous injection of C^{14}-labeled bicarbonate.

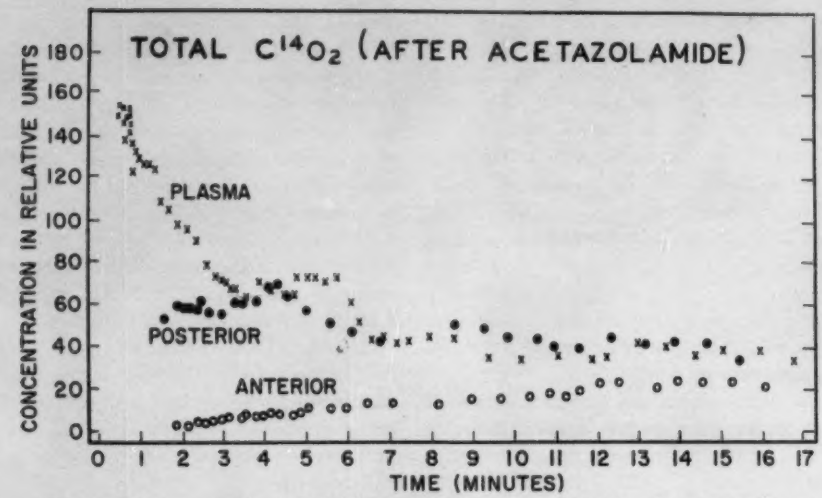

Fig. 2.—The concentration of C^{14}-labeled total carbon dioxide in the plasma, posterior and anterior chambers of the eyes of rabbits 15 minutes after administration of acetazolamide at various intervals after the injection of C^{14}-labeled bicarbonate.

humor is reduced but temporarily after administration of acetazolamide. By chance, the maximum effect of the drug, as will become evident later, is manifest after about this time interval.

A comparison of the data shown in Figures 1 and 2 indicates that the rate of decrease of radioactive CO_2 in the plasma of treated and untreated animals is indistinguishable, but the concentration of total labeled CO_2 in the posterior chamber of rabbits given acetazolamide is much less than in untreated animals. The half-turnover time ($t_{\frac{1}{2}}$) in the posterior chamber would appear to be of the order of two minutes, or at least 10-15 times less than in untreated rabbits.

The turnover rate in the anterior chamber is also depressed but probably to a less extent.

The time course of the inhibiting effect of acetazolamide on the turnover of bicarbonate in the posterior and anterior aqueous humors was determined. Figure 3 shows the concentration of total CO_2 in the posterior and anterior chambers (where the concentration in the plasma two minutes after administration of radioactive bicarbonate is arbitrarily set at 100) plotted against the time after giving acetazolamide. Each point on the graph represents an average of at least four eyes, and those after 10 or 15 minutes, at least eight eyes. The results indicate that the maximum inhibiting effect of acetazolamide in both the posterior and anterior chambers occurs at approximately 15 minutes after the injection of the drug. The graph shows also that the turnover of bicarbonate in the aqueous humor of the posterior chamber has almost returned to normal after an hour and that in the anterior

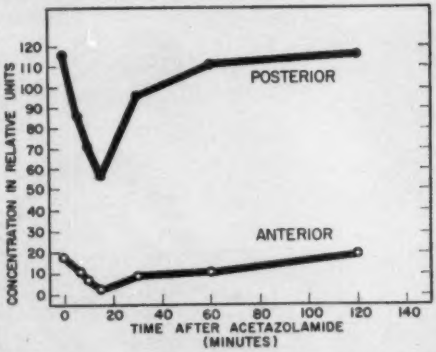

Fig. 3.—The concentration of C^{14}-labeled total carbon dioxide in the posterior and anterior chamber two minutes after the injection of C^{14}-labeled bicarbonate at various periods after administration of acetazolamide.

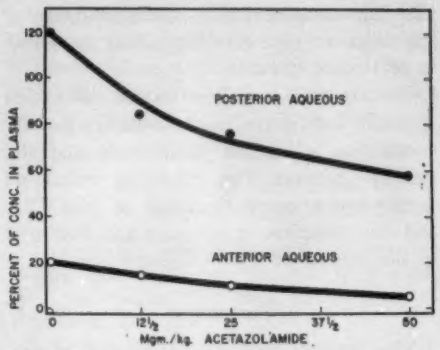

Fig. 4.—The concentration of C^{14}-labeled total carbon dioxide in the posterior and anterior chamber two minutes after the injection of C^{14}-labeled bicarbonate and 15 minutes after administration of varying doses of acetazolamide.

aqueous within two hours after the animals received acetazolamide.

The relationship between inhibition of turnover of total CO_2 and the dose of acetazolamide administered is shown in Figure 4. The concentration of the isotope in the aqueous humors was determined 15 minutes after the animals were given the drug and two minutes after the injection of radioactive bicarbonate. The concentration is expressed as a percentage of that in the plasma at the same time. The inhibition of turnover approaches a maximum asymptotically with dose.

A number of experiments were performed in which acetazolamide was administered topically or subconjunctivally. In the first instance 1 drop of 5% solution of the drug was applied per minute over a period of 15 minutes, and in the second 0.15 ml. of a saturated solution, pH 9, was injected subconjunctivally 8 to 15 minutes prior to giving the labeled bicarbonate. No inhibition was observed in any of the animals.

It is interesting to note that the concentration of labeled CO_2 in the anterior chamber of the eyes of animals receiving acetazolamide by subconjunctival injection was above normal—a result easily accounted for on the basis of increased permeability of the iris vessels because of the irritating effect of the injection. Despite the possibility of back-diffusion into the plasma, the concentration of bicarbonate in the posterior chamber after two minutes was found to exceed that of the plasma by approximately 20%.

Comment

The turnover of total CO_2 between plasma and aqueous humor as determined by isotopically labeled bicarbonate involves the separate rates of diffusional exchange across the blood aqueous barriers of free CO_2, bicarbonate ion, and undissociated carbonic acid. Unlike the situation for such ions as sodium and chloride, the characteristics of the blood aqueous barriers are not the sole factors controlling the turnover rate; for the bicarbonate system the rate of conversion of carbon dioxide to bicarbonate also influences the rate.

The rapidity of the turnover of total CO_2 in normal animals as observed in the present experiments and the depression of the turnover by acetazolamide we interpret as follows: Normally free CO_2 diffuses rapidly from the blood across the stroma and epithelium of the ciliary processes or, in the instance of the anterior chamber, by way of the iris vessels. In transit, labeled CO_2 exchanges for unlabeled CO_2 where the former is hydrated to form labeled bicarbonate. The bicarbonate ion, in effect, becomes "trapped" in the aqueous humor to the extent that its diffusibility into the blood is less than that of free CO_2. This conversion of labeled CO_2 to labeled bicarbonate probably occurs at a very rapid rate in normal animals and has the effect of reducing the concentration of labeled CO_2 available to diffuse back to the blood. In other words, the trapping action tends to maintain the gradient of free $C^{14}O_2$ between blood and aqueous at close to that prevailing initially until the total labeled CO_2 has almost reached steady-state level. The contribution of free carbonic acid is believed to be small because of its low concentration.

Acetazolamide presumably suppresses the turnover through interference with the trapping mechanism, i. e., by slowing the con-

version of carbon dioxide to bicarbonate through inhibition of carbonic anhydrase, the enzyme in the ciliary epithelium which normally catalyzes the reaction ($C^{14}O_2 + H_2O \rightleftarrows HC^{14}O_3^- + H^+$). The diffusion rates are probably not altered by the drug (Green[6]). This explanation of the mechanism of action is in accord with that postulated for other tissues.

That the depression of the CO_2 turnover in the aqueous humor is not caused primarily by a lack of labeled $C^{14}O_2$ in the blood through a depression in the rate of conversion of the $HC^{14}O_3$ to $C^{14}O_2$ is indicated from results of an experiment in which the radioactivity of expired CO_2 in normal rats and those given acetazolamide in doses similar to the ones employed in the present study was found to be indistinguishable.* Furthermore, the magnitude of the inhibition of turnover is much greater than could be accounted for from the relatively greater decrease in the absolute concentration of bicarbonate in the posterior chamber compared to the plasma.

The conclusion that the rapid turnover is due chiefly to diffusional exchange of CO_2 with subsequent conversion to HCO_3 ion is contrary to that of Green and Sawyer,[7,8] who have also investigated the turnover of total CO_2. They believe that the observed turnover rate is a measure of the rate of penetration of the bicarbonate ion itself.

The results obtained with acetazolamide in the present study also lead to conclusions different from those reached by Green and Sawyer, who made their measurements of the turnover of CO_2 only at the one time period (45 minutes) after administration of the drug. From the curve showing the time course of the inhibiting action of acetazolamide it is apparent that most of the effect had disappeared within 45 minutes. Thus while the results in the two laboratories agree that there is little effect from acetazolamide after 45 minutes, we conclude that this compound is a potent inhibitor of the turnover of total CO_2, albeit the effect is of limited duration.

The question of the extent to which carbonic anhydrase participates in the accumulation of excess bicarbonate and the relation between the inhibiting effect of acetazolamide on the turnover of total CO_2 and the reduction in pressure and flow will be the subject of a subsequent paper.

* These experiments were performed for us by Dr. James L. Spratt in Dr. George V. Leroy's Laboratory at the University of Chicago, the School of Medicine.

Summary

The accumulation of C^{14}-labeled carbon dioxide and bicarbonate ion (total carbon dioxide) in the aqueous humor of the posterior and anterior chambers after parenteral administration of C^{14}-labeled bicarbonate in rabbits has been determined.

Within less than one minute after intravenous injection, the concentration of total labeled carbon dioxide in the posterior aqueous exceeds that of the plasma by approximately 20%. Because of the rapidity of the entrance into the posterior chamber no quantitative value for the turnover rate could be calculated. The turnover in the anterior chamber was much less rapid and occurred at a rate corresponding roughly to a half-life of 10 minutes.

The intravenous administration of 50 mg. of acetazolamide (Diamox) per kilogram was followed by a marked inhibition in the turnover rate, especially in the posterior chamber.

The inhibitory effect of acetazolamide approached a maximum asymptotically with dose of the drug.

Maximal inhibition following a dose of 50 mg. of acetazolamide per kilogram occurred after 15 minutes; after one hour the turnover rate had returned almost to the normal level.

The high rate of turnover of total carbon dioxide between plasma and posterior aqueous was accounted for on the assumption that labeled free carbon dioxide diffuses with great rapidity into the aqueous, where it is hydrated to form the more slowly diffusing labeled bicarbonate ion, i. e., be-

comes "trapped." The reduction in the turnover rate produced by acetazolamide was believed to result from an inhibition of carbonic anhydrase, the enzyme concerned with the conversion of CO_2 to HCO_3.

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Ocular Manifestations of Occlusive Disease of the Vertebral-Basilar Arterial System

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Ocular symptoms and signs occur frequently in occlusive disease of the vertebral-basilar arterial system. Now that treatment has been improved and has been found useful in selected cases, careful studies and exact diagnoses assume more than academic interest in the management of cerebrovascular disease. Ocular symptoms develop in a number of patients with insufficiency within this vascular system as the initial or primary manifestation of their disease. Therefore, the ophthalmologist must be thoroughly familiar with this vascular disorder.

In previous publications,[19,25] the term "syndrome of intermittent insufficiency of the basilar arterial system" was introduced. As used in the present report, "insufficiency of the vertebral-basilar arterial system" is a clinical diagnosis made on the basis of recurrent transient episodes of focal neurologic impairment resulting from periods of inadequate blood flow through the vertebral, basilar, and posterior cerebral arteries and their branches. The symptoms include various combinations of dizziness, vertigo, blurred vision, diplopia, dysarthria, dysphagia, weakness of the limbs, numbness, and confusion. The symptoms frequently are bilateral or may alternate from side to side. Most episodes last from 5 to 15 minutes, but their duration may vary from several minutes to several hours. Objective neurologic signs are present during an attack but are characteristically absent between episodes. In some instances, minor residual signs, such as nystagmus, may persist.

It is sometimes difficult to determine by clinical methods exactly when occlusion within the vertebral-basilar arterial system develops in a patient with symptoms of intermittent insufficiency. When significant neurologic abnormalities are persistent or become progressive, the patient is considered to have a cerebral infarct and a clinical diagnosis is made of "thrombosis within the vertebral-basilar arterial system."

Anatomic Aspects

An understanding of the anatomy is essential in recognizing and interpreting this clinical syndrome. The basilar artery is formed by the right and left vertebral arteries, which meet at the lower border of the pons. The basilar artery runs forward and upward in the midline of the pons and bifurcates into the two posterior cerebral arteries at the upper border of the pons. Each posterior cerebral artery runs laterally and then, after receiving the posterior communicating artery, turns backward along the lower mesial surface of the cerebral hemisphere to supply portions of the temporal and occipital lobes.

Each posterior cerebral artery normally receives a posterior communicating artery from the internal carotid artery of the same

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Fellow in Ophthalmology, Mayo Foundation (Dr. Minor); Section of Ophthalmology (Dr. Kearns); Section of Neurology (Drs. Millikan and Siekert), and Section of Pathologic Anatomy (Dr. Sayre), Mayo Clinic and Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

side, forming the posterior portion of the circle of Willis. The high frequency of deviations from the normal pattern of the circle of Willis and the resultant alteration of the potential cerebral collateral circulation are poorly described in many textbooks of anatomy. In a review of three large series of anatomic studies of the circle of Willis in adults without aneurysms, Dandy found a normal circle of Willis in barely 50% of the cases. In 8% of the total group, an interruption was present in the circle of Willis. Deviation from the normal size of the component vessels, most commonly in the posterior part of the circle, was present in more than 40% of the cases. Vander Eecken and Adams pointed out that, in addition to the circle of Willis, the meningeal arterial anastomoses and the capillaries of the brain play a role in adjusting the hemodynamics after cerebrovascular occlusion. This variability in blood supply is probably one of the factors that accounts for the different combinations of signs and symptoms in patients with occlusive disease of the vertebral-basilar system.

Review of the Literature

Prior to 1940, little was written concerning diseases of the basilar artery. Even recently published textbooks dealing with cerebrovascular disease, ophthalmology, and neuro-ophthalmology devote little or no space to the subject. Most authors state the commonly held opinion that obstruction of the basilar artery causes death within a short time.

Necropsy data in cases of blindness or bilateral homonymous hemianopsia resulting from occlusive disease within the vertebral, basilar, or posterior cerebral arteries were reported by several investigators,[14,15,22,30] beginning in 1941. Several other authors reported on patients who had bilateral field defects thought clinically to be due to occlusive disease within the posterior cerebral arteries.[8,17,23,29,32]

In 1946, Kubik and Adams made a clinical and pathologic study of occlusion of the basilar artery, presenting 11 fatal and 4 nonfatal cases of thrombosis of the basilar artery. Transient premonitory symptoms prior to the fatal occlusion were noted in the histories of 8 of the 11 patients.

Denny-Brown [6] reported a case of basilar-artery occlusion in 1951, in which he attributed the fluctuating signs and symptoms to a state of episodic insufficiency in the circle of Willis. In 1953, he discussed [7] the basilar-artery syndromes. Biemond reported four cases of basilar-artery thrombosis in 1951. In 1953, Fisher and Cameron reported the case of a 70-year-old woman with a clinical diagnosis of incipient basilar-artery thrombosis whose recurrent transient cerebral attacks were controlled by administration of anticoagulants; they stressed the frequency and importance of such transient warning phenomena in cerebrovascular thrombotic processes. Campbell also reported on a patient whose episodic symptoms of a similar nature ceased after anticoagulant therapy. He stated that occlusion of the basilar artery with disturbance of function in the regions of the brain it supplies is known as the "basilar-artery syndrome." Corday and associates defined the entity of "cerebral vascular insufficiency" as a generally transient and reversible insufficiency of the cerebral blood flow caused by a decrease in systemic blood pressure.

Kubik and Adams commented that basilar-artery thrombosis is not always fatal. In 1953, Freeman and co-workers reported on a patient who had survived for 10 months after what was diagnosed clinically as basilar-artery occlusion. Siekert and Sayre, in 1954, reported the necropsy findings concerning a patient who lived eight months after clinical evidence of basilar-artery occlusion before dying of a myocardial infarct.

Silversides reported 22 cases of basilar-artery thrombosis in 1954. Nine of the patients in this series had recurrent premonitory symptoms prior to the terminal basilar-artery thrombosis. He suggested that such symptoms might be due to periodic insufficiency of blood flow to the brain stem.

Millikan and Siekert emphasized the concept of the syndrome of intermittent insufficiency of the basilar arterial system and presented 10 cases, including 5 in which ocular findings were present, to document the condition. Three of these ten patients subsequently died of basilar-artery thrombosis, the diagnosis being substantiated at necropsy in each instance. Their report suggested that this syndrome occurs more commonly than is generally realized and frequently precedes basilar-artery thrombosis. In a subsequent article, the same authors[24] presented a group of 28 fatal cases of basilar-artery thrombosis; such premonitory symptoms of cerebrovascular insufficiency were noted in 20 of these cases. The varying signs and symptoms were correlated with the location of the ischemia or infarction in the tissues supplied by the basilar artery as follows: 1. Dimness of vision results from involvement of the calcarine regions of the occipital lobes, which receive their blood supply from the posterior cerebral arteries, the terminal branches of the basilar artery. 2. Diplopia and nystagmus result from involvement of the cranial nerves concerned with rotation, the medial longitudinal bundle, and the vestibular nuclei. 3. Pupillary abnormalities result from lesions in the mesencephalic tegmentum and tectum and the descending sympathetic fibers. 4. Pseudobulbar phenomena, such as dysarthria and dysphagia, are caused by involvement of the corticobulbar fibers to the nuclei of the lower cranial nerves. 5. Weakness of the limbs results from involvement of the corticospinal tract. 6. The peripheral type of facial weakness results from lesions in the facial nuclei or intrapontine facial nerve fibers. 7. Alteration in consciousness is presumably due to involvement of ascending reticular pathways.

Gross and associates reported on two patients with basilar-artery occlusion whose only ocular findings were small nonreactive pupils. De Hollander reported a case of basilar-artery thrombosis in which pathologic examination suggested that the thrombosis may have followed an episode of arteritis. Ford reported the case of a boy who had intermittent episodes of nystagmus, diplopia, and blurred vision resulting from obstruction of the vertebral arteries caused by a defect in the odontoid process that allowed excessive mobility of the second cervical vertebra. Ford and Clark reported on two patients who had basilar-artery thrombosis after manipulation of the neck. Meyer and co-workers recorded the effect of 70-degree postural tilting on the systemic blood pressure and the electroencephalogram in patients with histories of severe basilar-artery insufficiency. The decrease in blood pressure was significantly greater in these patients than it was in a control group without known cerebrovascular disease.

Present Study

This study is based on 183 cases of occlusive disease of the vertebral-basilar arterial system diagnosed at the Mayo Clinic during the years 1953 through 1956. An attempt was made to include every patient who received such a diagnosis during this four-year period. The diagnosis was established in each instance by a neurologic consultant after a detailed history and neurologic examination.

Patients who were thought to have occlusive disease of both the carotid and the basilar arterial systems were excluded from this study, as were those patients with isolated thrombosis of the posterior inferior cerebellar artery.

The patients were divided arbitrarily into two groups as described in previous publications,[19,24] namely (1) those with a clinical diagnosis of thrombosis within the vertebral-basilar system (124 patients) and (2) those with a clinical diagnosis of intermittent insufficiency of the vertebral-basilar system (59 patients). Patients who ultimately exhibited a significant residual neurologic deficit after an episode of insufficiency within the vertebral-basilar system were considered to have had an infarct and were placed in the first group. The severity of the lesions in patients in the

"thrombosis" group ranged from minor infarcts caused by transient circulatory insufficiency to complete basilar-artery occlusion resulting in death.

Necropsy findings were available in 19 cases. One additional patient was found to have basilar-artery thrombosis at necropsy elsewhere.

Clinical Observations

Of the 183 patients in this series, 127 (70%) were men. The ages of the entire group of patients ranged from 38 to 83 years, with an average age of 61 years. A total of 83% of the patients were between 50 and 70 years of age, while slightly more than 50% were in the age group of 55 through 65 years.

Hypertension was noted in 32 of the 124 cases of thrombosis and in 16 of the 59 cases of intermittent insufficiency of the vertebral-basilar arterial system. Of the 183 patients, 7 were known to have had previous myocardial infarction; 4 others had auricular fibrillation, and 3 had coronary insufficiency. One of the patients with auricular fibrillation had rheumatic endocarditis. One patient had aortic stenosis. Four patients had polycythemia, and seven had diabetes mellitus. Six patients experienced basilar-artery thrombosis after general anesthesia for surgical procedures; one of these died.

Episodes of intermittent insufficiency in one patient appeared to be associated with periods of coronary insufficiency. In general, however, correlation apparently did not exist between attacks of intermittent insufficiency and exertion or any specific activities.

A total of 100 (80%) of the 124 patients with a clinical diagnosis of thrombosis within the vertebral-basilar arterial system had experienced known episodes of intermittent insufficiency prior to the thrombosis. Of the 24 patients without such a history, 6 had thrombosis after general anesthesia, 2 were treated with anticoagulants after their first attacks and had no subsequent difficulty, and 1 was a 38-year-old man with a pheochromocytoma. Eleven of the other patients who had no premonitory episodes had severe neurologic disturbances: Four of these 11 noted sudden onset of bilateral homonymous hemianopsia, three had persistent ataxia and diplopia in association with internuclear ophthalmoplegia, and four died shortly after their admission to the hospital. Three patients who had single thrombotic episodes recovered uneventfully without the benefit of anticoagulant therapy and had no known episodes of intermittent insufficiency. A 72-year-old patient who was not treated with anticoagulants deteriorated slowly without the occurrence of any specific episodes of insufficiency.

Ocular Abnormalities

Some ocular abnormality was present in 144 (79%) of the patients in this study. It is possible that this figure is disproportionately high. The majority of the diagnoses were made clinically, without necropsy verification, and the presence of ocular findings was sometimes a deciding factor in establishing the diagnosis. A patient without ocular findings was more likely to receive a tentative diagnosis and thus be excluded from this study.

Visual loss was the only complaint of 12 of the patients; 9 of these had bilateral homonymous hemianopsia, and 2 had unilateral homonymous hemianopsia. A total of 43 other patients included some visual disturbance as one of their chief complaints. In this last group, 14 were found to have bilateral homonymous hemianopsia and 8 had unilateral homonymous hemianopsia.

Blurred vision involving the entire visual field of both eyes was the commonest ocular symptom, occurring in 73 (40%) of the 183 patients. Of the 59 patients with intermittent insufficiency, 27 (46%) had episodes of blurred vision and 10 (17%) complained of transient homonymous hemianopic visual-field defects. A few of the patients with histories of intermittent episodes of blurred vision also had some transient periods of total blindness. Longer

periods of blindness were noted by five patients.

Diplopia was a complaint of 13 of the patients with intermittent insufficiency and of 37 of the patients with thrombosis. Twelve of these latter thirty-seven patients had the diplopia as a result of internuclear ophthalmoplegia; in three instances, the diplopia was associated with paresis of conjugate gaze; two patients had skew deviations, and one had palsy of the sixth cranial nerve as the cause of diplopia; the exact cause of the diplopia in the remaining nineteen patients was not readily apparent.

Nystagmus was noted in 13 of the 124 patients with thrombosis, not including those patients with internuclear ophthalmoplegia. Five patients in the group of fifty-nine with intermittent insufficiency had nystagmus.

Internuclear ophthalmoplegia was found in 15 patients. Six of these fifteen patients also had bilateral homonymous hemianopsia. One had complete right homonymous hemianopsia, one had incomplete homonymous hemianopsia, and one had right homonymous hemianopic scotomas. Six of these fifteen patients had clear-cut unilateral internuclear ophthalmoplegia, and three had typical bilateral internuclear ophthalmoplegia. One other patient had paresis of the left lateral rectus muscle as well as right internuclear ophthalmoplegia. One had bilateral paresis of conjugate gaze in addition to left internuclear ophthalmoplegia. The remaining four patients had paresis of conjugate gaze to one side with internuclear ophthalmoplegia on the other. Nearly all of these patients complained of diplopia and ataxia.

Paresis of lateral conjugate gaze was present in 10 patients who were not thought to have internuclear ophthalmoplegia. One of these patients also had limitation of vertical conjugate gaze. Conjugate deviation of the eyes to the left was noted in two patients. The oculorotary findings often varied from day to day and, in some instances, from hour to hour.

Mention of pupillary abnormalities seldom was made in the records reviewed for this study. Anisocoria occasionally was noted, and one patient was thought to have Horner's syndrome.

Ocular Findings in Occlusive Disease of the Vertebral-Basilar Arterial System

	No.	
Total patients		183
Patients with ocular symptoms and signs		144
Episodes of blurred vision	73	
Diplopia	50	
Bilateral homonymous hemianopsia	26	
Unilateral homonymous hemianopsia	21	
Nystagmus (without internuclear ophthalmoplegia)	18	
Transient homonymous hemianopsia	15	
Internuclear ophthalmoplegia	15	
Paresis of conjugate gaze	10	
Distorted vision	8	
Ptosis	8	
Conjugate deviation	2	

Ptosis was noted in eight patients. Distortion of vision was reported by eight patients; this was most commonly in the form of scintillating scotomas. The ocular abnormalities are summarized in the accompanying table.

Report of Cases

Six cases have been selected to illustrate some of the characteristic ocular findings that may occur in occlusive disease of the vertebral-basilar system.

CASE 1.—A 63-year-old minister was admitted to the hospital in July, 1955. Four days prior to admission, he became dysarthric during church school. He had a short episode of confusion later that morning and unintentionally repeated part of his sermon. He had several more periods of confusion during the next three days. One day prior to admission, he had a five-minute episode of left hemiparesis, followed on the day of admission by persistent confusion, dysarthria, dysphagia, and difficulty with vision.

Examination revealed a blood pressure of 180 mm. of mercury systolic and 90 mm. diastolic. The patient was confused, disoriented, and moderately dysarthric. Babinski's sign was present on the right, and bilateral homonymous field defects were found (Fig. 1). A diagnosis of basilar-

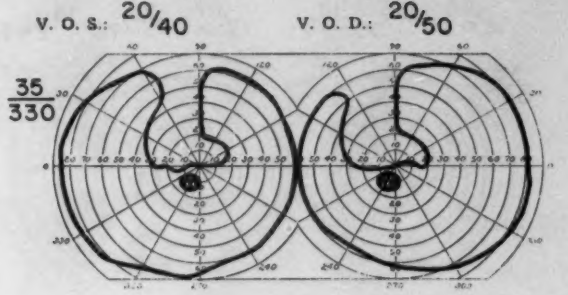
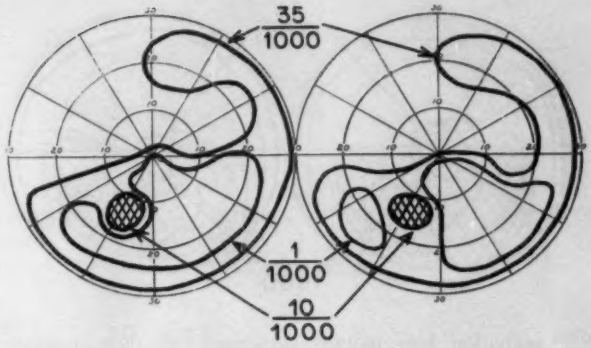


Fig. 1 (Case 1).—Bilateral homonymous hemianopsia in a patient who had a typical history of thrombosis of the vertebral-basilar arterial system.



artery thrombosis was made by the neurologists, and anticoagulant therapy was started. Some mental clearing occurred during the first week of hospitalization, but bilateral strongly positive Babinski's signs subsequently developed; he became nonresponsive and died after 18 days of hospitalization. The prothrombin time had been kept consistently within the therapeutic range.

Necropsy revealed pronounced cerebral arteriosclerosis, with thrombosis of both the right vertebral and the basilar artery. The posterior communicating arteries could not be demonstrated. Recent infarcts were present in one temporal lobe and both occipital lobes, as well as in the pons, cerebellum, and basal nuclei. Old infarcts were found in the basal nuclei and the frontal lobes.

CASE 2.—A 65-year-old man came to the Mayo Clinic in February, 1957, because of transient dizzy spells of four months' duration. The dizziness usually lasted several minutes and apparently was unrelated to activity. Three weeks before he came to the clinic, blurred vision first developed. Two weeks later, he began to have spells of confusion and loss of memory.

While being examined in the Section of Ophthalmology at the clinic, he had an episode of severe dizziness, nausea, and vomiting. He had noted a short episode of dysarthria earlier in the day. The perimetric fields demonstrated bilateral homonymous hemianopsia (Fig. 2). A diagnosis of intermittent insufficiency and thrombosis within the vertebral-basilar arterial system was suspected by an ophthalmologist, and the patient was admitted to the hospital for neurologic evaluation, which revealed only slight bilateral ataxia. Long-term anticoagulant therapy was started. Further episodes of dysarthria or dizziness did not occur.

The patient was dismissed from the hospital two weeks after his initial registration.

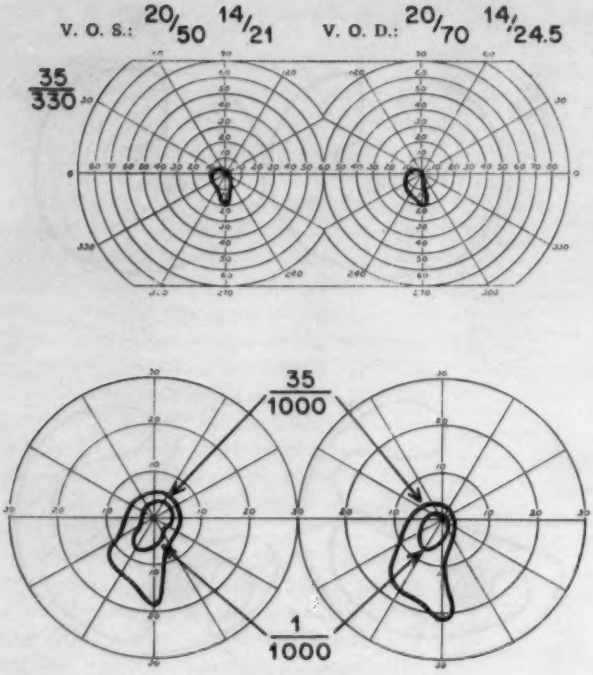


Fig. 2 (Case 2).—Bilateral homonymous hemianopsia with a small residual central isle of vision in a 65-year-old man who had numerous episodes of basilar-artery insufficiency.

Reexamination four months later revealed no significant changes in the size of the small isle of remaining vision.

CASE 3.—A 60-year-old woman was admitted to the hospital in December, 1955, complaining of episodes of poor vision, numbness, and mental confusion. These attacks lasted from several minutes to an hour and had been present for three days. The tingling sensation involved the upper lip, tongue, hands, wrists, and feet and affected the right side of the body more often than the left. Occasionally, in association with nausea and loss of balance, she thought her eyes were "jumping." She also had spells of "shimmering" vision and saw flashes of light, described as checkerboards, Venetian blinds, and large colored balls. She was known to have hypertension and diabetes mellitus.

Examination revealed a blood pressure of 210/110, mild ataxia, mildly hyperactive right deep tendon reflexes and bilateral Babinski's signs. Bilateral homonymous hemianopic scotomas were present, although the visual acuity was 20/20 and 14/21 in each eye (Fig. 3).

A diagnosis was made of intermittent insufficiency and thrombosis within the vertebral-basilar system. Bishydroxycoumarin (Dicumarol) therapy was started. The attacks stopped when the prothrombin time was maintained between 30 and 40 seconds (normal, 18 to 20 seconds). She was dismissed after 19 days but returned almost immediately because of recurrence of the transient spells of numbness of the face and both hands, confusion, slurred speech, dizziness, and shimmering vision. The prothrombin time was 21 seconds. The attacks again were controlled when larger doses of bishydroxycoumarin were administered and the prothrombin time reached the therapeutic range. Examination of the visual fields after five weeks of treatment revealed a slight decrease in the size of the scotomas.

CASE 4.—A 52-year-old steam engineer came to the clinic in December, 1953. Dur-

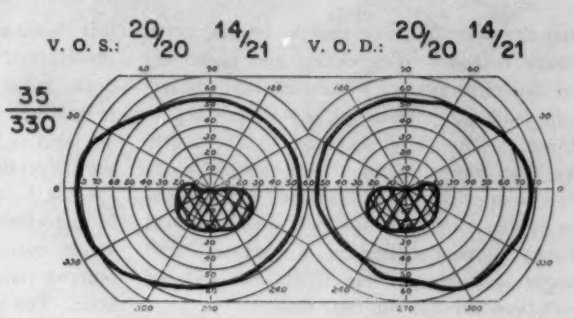
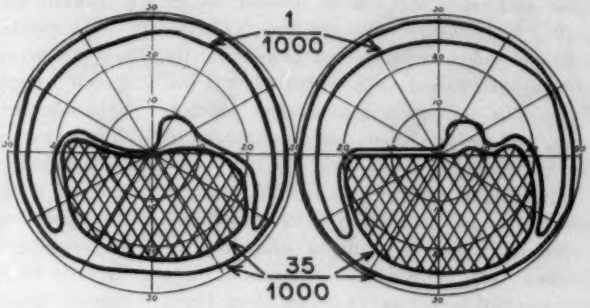


Fig. 3 (Case 3).—Bilateral homonymous hemianopic scotomas in a 60-year-old hypertensive diabetic woman with a three-day history of intermittent insufficiency within the vertebral-basilar arterial system.



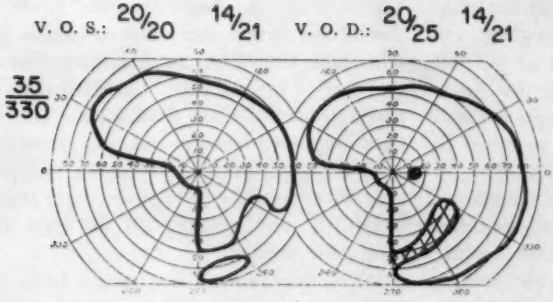
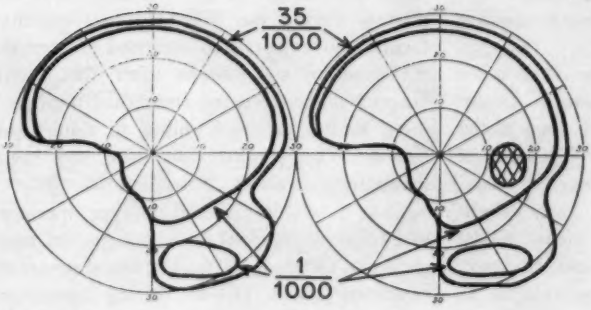


Fig. 4 (Case 4).—Bilateral homonymous hemianopic field defects in a 52-year-old man whose intermittent insufficiency and thrombosis within the vertebral-basilar arterial system were associated with polycythemia.



ing the preceding two months he had noted many episodes of prickling and numbness of the right side of the mouth and the left arm and leg. These attacks lasted two to three minutes and occurred as frequently as five times a day. Left homonymous hemianopsia had developed five weeks prior to registration, and for two weeks he had noted occasional nausea. Clumsiness and slight weakness of the right arm and leg had been present for four days.

Examination revealed bilateral homonymous hemianopsia (Fig. 4). Hyperactive knee and ankle jerks were present on the right. The erythrocyte count was 5,470,000 cells per cubic millimeter of blood, and the volume of packed cells (hematocrit) was 54%. His symptoms abated after phlebotomy, and he was dismissed to the care of his home physician.

The patient returned 18 months later, at which time he complained of recurrent episodes of transient diplopia and loss of balance, both of one year's duration. The diplopia had been present two or three times weekly, each episode lasting about five minutes. Transient episodes of tingling and numbness about the mouth and of the left arm and leg had been present for more than 18 months. His home physician had done repeated phlebotomies in an effort to keep the value for hemoglobin less than 16 gm. per 100 ml. of blood. Examination revealed left homonymous hemianopsia and mild weakness and incoordination on the right side. Results of hematologic studies were within normal limits. A diagnosis was made of intermittent insufficiency and thrombosis within the vertebral-basilar system, and long-term bishydroxycoumarin therapy was started.

The patient returned to the clinic after six months of anticoagulant therapy. Diplopia and perioral tingling had been noted only once during that period. Episodes of transient weakness had not occurred. Neurologic examination disclosed only slight ataxia. Examination of the visual fields, however, showed crescentic right homonymous hemianopic scotomas in addition to left homonymous hemianopsia, indicating involvement of the left as well as the right optic radiations. The patient was advised to continue the long-term anticoagulant therapy and to have his home physician control the polycythemia with phlebotomies.

CASE 5.—An obese 54-year-old man came to the clinic in April, 1956, because of a single episode of dizziness, sweating, and blurred vision that had lasted for about one hour. The patient was extremely apprehensive. The blood pressure was 172/100. He was given antihypertensive therapy and instructions for losing weight.

One month later, he was admitted to the hospital because of visual blurring, slurred speech, dysphagia, difficulty in using the right side of the body, and a staggering gait, all of two weeks' duration. Examination revealed incomplete right homonymous hemianopsia, complete paralysis of upward gaze, nystagmus on downward gaze, excessive convergence for near vision, poor pupillary response to light, dysarthria, moderate euphoria, moderate ataxia, and mild right hemiparesis. A diagnosis was made of thrombosis within the vertebral-basilar system, and long-term anticoagulant therapy was started immediately. Left lateral rectus palsy developed four days later. The patient improved slowly and was dismissed after 19 days of hospitalization, at which time the excessive convergence, slight ataxia, dysarthria, and weakness of the right arm were still present.

When reexamined five weeks later, the patient apparently had improved except for the development of bilateral homonymous field defects (Fig. 5), which improved slightly during the following two months. Ocular movements had returned to normal. Examination six months after the initial hospitalization revealed significant improvement in the patient's ability to think and reason. The prothrombin time had been maintained at about 35 seconds.

CASE 6.—A 56-year-old linotype operator had bilateral inguinal hernias repaired surgically in October, 1956. The blood pressure remained above 110/65 during operation

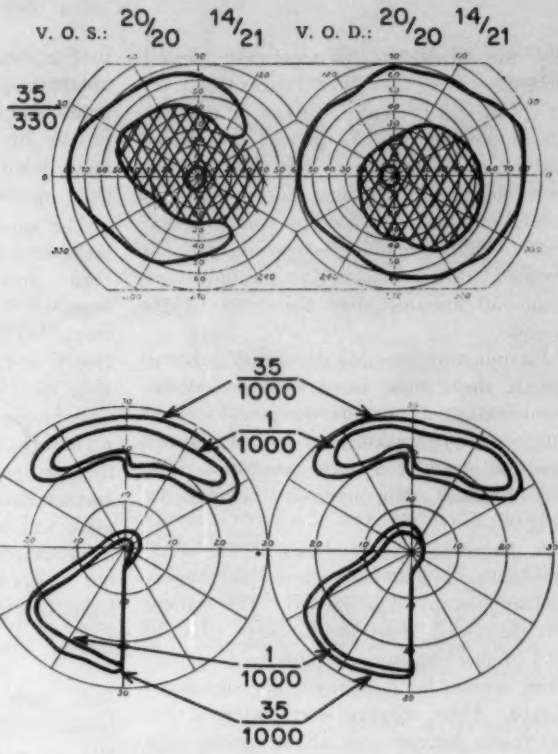


Fig. 5 (Case 5).—Bilateral homonymous hemianopsia in an obese hypertensive 54-year-old man who had a single premonitory episode of intermittent insufficiency within the vertebral-basilar system about two weeks prior to the onset of permanent field defects.

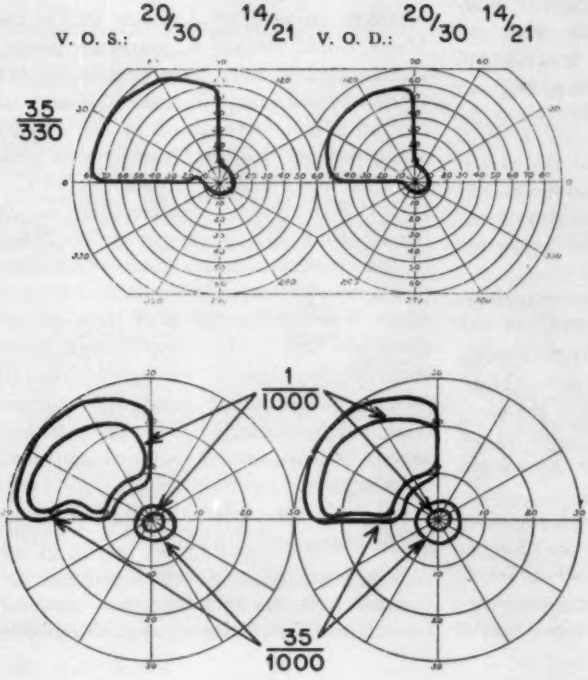


Fig. 6 (Case 6).—Bilateral homonymous hemianopic field defects in a 56-year-old man who had thrombosis within the vertebral-basilar arterial system after surgical repair of bilateral inguinal hernias.

and the immediate postoperative period. Five days after operation transient blurring of vision was present for about 30 minutes. The following day the patient complained that he could not see to one side, and the next morning he became unconscious for several minutes. The blood pressure was normal. While regaining consciousness, he vomited. Blurred vision was the only complaint 30 minutes after the onset of the episode.

Examination revealed drowsiness, slurred speech, slight right facial weakness, downward-beating nystagmus on gaze to either side, moderate weakness of both downward gaze and (later) conjugate gaze to the right, and bilateral homonymous hemianopsia (Fig. 6).

A diagnosis of thrombosis in the vertebral-basilar system was made, and anticoagulant therapy was started. The patient was dismissed from the hospital after 10 days of this treatment. Visual fields plotted three weeks later showed no significant change. Four months later, bilateral homonymous hemianopsia, slight spastic right hemiparesis, and slight difficulty with coordination of the right extremities were still present, but the patient was working full time. He was still taking bishydroxycoumarin.

Comment

Early diagnosis of occlusive disease of the vertebral-basilar arterial system often depends on the recognition of associated ocular signs.

Premonitory episodes of intermittent insufficiency were present in 80% of the patients with clinical evidence of thrombosis within the vertebral-basilar system. Thus, early diagnosis is of importance in the institution of therapy in selected cases in an attempt to prevent permanent neurologic damage.

The development of bilateral homonymous field defects and the presence of signs of a lesion in the brain stem, such as internuclear ophthalmoplegia, appear to be diagnostic of basilar-artery occlusion. Nearly half of the 15 patients with internuclear ophthalmoplegia also had bilateral homonymous field defects; approximately one-third of the 26 patients with bilateral homonymous hemianopsia had associated internuclear ophthalmoplegia.

The evaluation of anticoagulant therapy is beyond the scope of this study; it has been presented in other communications.[20,21,27] However, anticoagulant drugs controlled the attacks of intermittent insufficiency in nearly every case in which they were used. A number of patients who had severe occlusive disease responded extremely favorably to these drugs. Anticoagulant therapy apparently was effective in checking further progression of the occlusive processes and in preventing further episodes of cerebrovascular insufficiency or thrombosis, but it was not effective in restoring neurologic function that already had been lost.

Summary

A study with particular reference to ocular signs and symptoms was made on 183 patients with occlusive disease of the vertebral-basilar arterial system seen at the Mayo Clinic during a four-year period. Ocular abnormalities were present in 144 (79%) of this group. Transient episodes of blurred vision were noted by 73 (40%) of the patients. Bilateral homonymous hemianopsia was found in 26 patients and unilateral homonymous hemianopsia in 21 others. Diplopia was present in 50 (27%) of the patients. Internuclear ophthalmoplegia was present in 15 patients, in 6 of whom it was unilateral; 6 of these 15 patients also had bilateral homonymous hemianopsia. Nystagmus was noted in 18 patients, not including those with internuclear ophthalmoplegia. Ten patients had paresis of conjugate gaze unaccompanied by internuclear ophthalmoplegia.

Six cases are reported to illustrate some of the characteristic findings.

It is important that ophthalmologists be familiar with the symptoms and signs of intermittent insufficiency and thrombosis

within the vertebral-basilar arterial system in order to recognize them as a warning threat not only to vision but to life itself.

Mayo Clinic.

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Fixation Pick and Scleral Depressor for Use in Operations of Retinal Detachment

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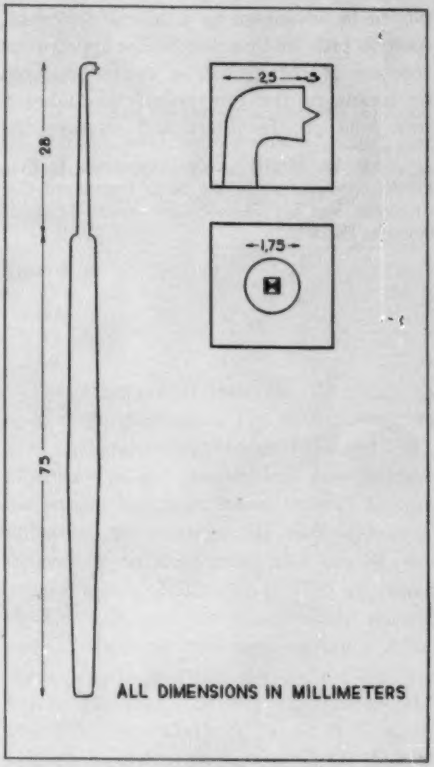
In cases of separation of the retina where this membrane is considerably elevated, a correct estimate of the accuracy with which surface diathermy is applied may prove very difficult, for no mark will then show in the fundus. As failure to achieve a permanent sealing of the existing breaks—either by means of coagulation alone or with the aid of a scleral buckling—could then follow, the importance of proper detection and localization of the affected areas cannot be overemphasized.

Transillumination of the eye with a special electrode has been advocated by Strampelli [4] as a valuable addition to ordinary ophthalmoscopic control. The glowing tip of the instrument is moved on the sclera until a small clear spot is seen to reach the retinal tear; current is then turned on, whereby a brown-gray pilot mark will be left at precisely the right place. A similar instrument has been used by Amenábar,[1] in conjunction with a bipronged scleral hook which serves to fixate the luminous end of the locator when the tear is transilluminated, and leaves a small indentation on the sclera. Schepens and co-workers,[3] in turn, recommend that a ball electrode be pressed on the sclera while one examines the fundus, until the rounded elevation of the choroid thus produced is seen to coincide with the break; the current is then switched on and a mark left on the scleral surface.

As, however, the globe must be rotated along the meridian which passes through the tear, *toward* the latter and *away* from the observer's eye, so that the tear becomes readily visible with the ophthalmoscope (upward, for instance, in the case of a peripheral tear located at 12 o'clock, while the beam of the ophthalmoscope is directed at the fundus from below, at 6 o'clock), one will find that the area to be transilluminated or depressed is ordinarily more



Fixation pick, scleral depressor, and marker for use in retinal detachment surgery. Adequate rotation of globe and precise location of tears may be achieved in cases where the retina is ballooned and too far removed from the choroid to be affected by surface diathermy.

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or less hidden from view. The tip of the compressing instrument may, and usually does, slip over the smooth scleral surface as soon as the rotation is reversed in order to expose the affected area, the exact position of which will thus be difficult to establish with absolute certainty. Since, besides, the sclera cannot be kept dry in such places as are concealed under the conjunctiva and Tenon's capsule, a neat coagulation mark may not always be produced by an electrode used as depressor (Lindner [2]).

A special instrument consisting of a slender steel shaft bent at right angles near its extremity, which bears a short and not very sharp point in the center of the terminal platform (Figure), has been employed to advantage as a scleral depressor, fixation pick, and marker,* The appropriate rotation of the eyeball is easily produced by means of the tiny point; this takes a firm hold on the sclera and obviates the need for a fixation forceps. In addition, it leaves a clearly recognizable, small indentation at the exact site where the coats of the eye have been depressed. The handle has been made shorter than in most ophthalmic instruments (75 mm. instead of the usual 90-100 mm.), in order that less interference may be encountered when a direct ophthalmoscope is used. The dimensions of the bent part of the shaft are such that sufficient depression of the sclera over a limited area may be accomplished with only light pressure.

Casilla de Correo 301.

*Made by Messrs. Lutz, Ferrando & Cía., Córdoba, Argentina, by the Storz Instrument Co., St. Louis, and by "Moria," Instruments d'Ophtalmologie, Paris.

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Neuropathology of the Trabeculum in Open-Angle Glaucoma

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This paper demonstrates the neuropathology of the trabeculum in both eyes of a case of "primary" open-angle glaucoma. For this study it was not only necessary to obtain the eyes of a clinically well-studied case of open-angle glaucoma that had had no surgery, I also needed the combination of a great amount of luck and some experience to get a complete and uniform stain of the delicate nerve fibers in the trabeculum of the anterior chamber.

Clinical History

A 78-year-old white man died on June 13, 1956, at this University Hospital with the diagnosis of adenocarcinoma of the rectum. He first came to this eye clinic on July 22, 1944, and was seen and followed as a patient of Dr. Harold F. Falls. At the first examination, his intraocular pressure was found to be O. D., 35 and O. S., 40 mm. Hg Schiøtz and his vision was O. D., 6/6; O. S., 6/6. The visual fields were normal. The diagnosis of "chronic noninflammatory" glaucoma was made. The patient was treated with pilocarpine eye drops 2% gtt. 1 q. i. d. O. U. His pressure for years was well controlled with this medication, and he was seen and checked at two-month intervals. No loss of vision or fields was observed.

An increase in the intraocular pressure was observed on May 9, 1950. His vision at that time was O. D., 6/6 and O. S., 6/6−1. The visual fields were still normal. The medication was then increased to pilocarpine 2% five times daily, and 24-hour tension studies were done on May 18, 1950:

	Mm. Hg	
Time	O. D.	O. S.
2:00 p. m.	26	26
4:00 p. m.	30	28
8:00 p. m.	22	19
Midnight	28	23
6:35 a. m.	28	25
9:00 a. m.	32	32

The 24-hour tension studies were repeated on Feb. 13, 1951, with a similar result, and a drinking water test was done at the same time (1,000 cc. of water at 6:30 a. m.):

	Mm. Hg	
Time, Min.	O. D.	O. S.
15	29	28
30	32	30
45	32	32
60	43	37

These tests confirmed the diagnosis of open-angle glaucoma. The patient was not very well controlled through 1952 and 1953. However, no eye surgery was done because the patient had been found to have a carcinoma of the rectum. He had abdominal surgery at different times and was in poor general health. His vision in 1953 was about O. U., 6/9, and his visual fields showed some peripheral loss and enlarged blind spots. The patient was seen for the last time before his death on Feb. 22, 1956. His vision then was O. D., 6/25 and O. S., 6/12. His intraocular pressure was O. U., 27 mm. Hg. The patient died on June 13, 1956, of metastasizing adenocarcinoma of the rectum. Both eyes were given injections after death with ammonium bromide formalin

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From the Department of Ophthalmic Surgery and the Laboratory of Neuropathology of the University of Michigan Medical Center.

(Cajal solution) and obtained for histological study at postmortem examination.

Method of Histological Examination

Half of both eyes were imbedded in paraffin, cut in serial sections, and stained with hematoxylin and eosin. Of the other halves, the areas with the anterior chamber filtration angle were isolated. Tangential sections [1] of the filtration angle were made on the freezing microtome. The methods with double impregnation and without reduction and the threefold method of del Rio Hortega [2] were used to stain these frozen sections.

All the illustrations of this paper are unretouched photomicrographs.

Histological Findings

Macroscopically both eyes were of normal size and shape. The anterior chambers were of normal depth, and the lenses were in their normal location. The pupils were miotic. The posterior part of the vitreous was liquified in both eyes, and a ring-shaped formation of abnormally dense vitreous was found attached to the peripheral retina and the posterior part of the ciliary body.

The microscopic pathology of both eyes of this patient was very similar, and it is therefore possible to discuss the histological findings in both eyes at the same time. The corneal epithelium was continuous but showed a somewhat irregular surface. Bowman's membrane, the corneal stroma, Descemet's membrane, and the corneal endothelium were normal in structure and thickness. The anterior chamber was of about normal depth, and the filtration angle was open. The results of the special stains in this area will be discussed later in the paper. Hematoxylin and eosin stains showed the trabeculum to be of rather dense structure and to contain pigment granules. Schlemm's canal was visible, but it seemed to contain very numerous cellular nuclei. The iris was normal. The ciliary body showed some fibrosis of its stroma and the ciliary processes. The ciliary processes also showed hyalinization in some of the fibrotic areas. The peripheral retina showed advanced cystoid degeneration in those areas to which the dense ring-shaped remnants of the anterior vitreous were attached. The central and intermediate retina showed a distinct atrophy of the nerve fiber layer with diffuse and local swelling and interruption of nerve fibers. There was also a distinct decrease of the number of ganglion cells of the ganglion-cell layer. All inner layers of the retina showed hypertrophy and proliferation of their glia (gliosis). The outer layers of the retina showed only slight atrophy. No glaucomatous cupping of the optic discs was found. However, both optic nerves were somewhat atrophic and many hyaline bodies [3,4] were found in the atrophic nerve fiber bundles in front of and behind the lamina cribrosa. The choroid was small and atrophic; the sclera was normal.

The histological studies of the areas of the filtration angles in the two eyes with use of the silver carbonate techniques allowed for a number of interesting findings. Again, it must be emphasized that these findings were virtually the same in the two eyes and that they are therefore discussed at the same time.

The angles were wide open, and the trabeculum as a whole was of normal shape and size in both eyes. The structure of the trabeculum, however, was definitely abnormal. The trabeculae were much coarser than normal, and the trabecular spaces were very small (Figs. 1, 2, and 10). Furthermore there was a tremendous increase of the number of endothelial cells of the trabeculum as well as Schlemm's canal. This was most marked in the scleral part of the trabeculum (Figs. 1, 2, and 10) and in the canal of Schlemm (Figs. 1, 2, and 11). Only slight or no proliferation of the trabecular endothelium was found in the uveal part of the trabeculum. The combination of an increase of the thickness of the single trabeculae and of the proliferation of the trabecular endothelium had resulted in a very dense structure of the trabeculum of both eyes (Figs.

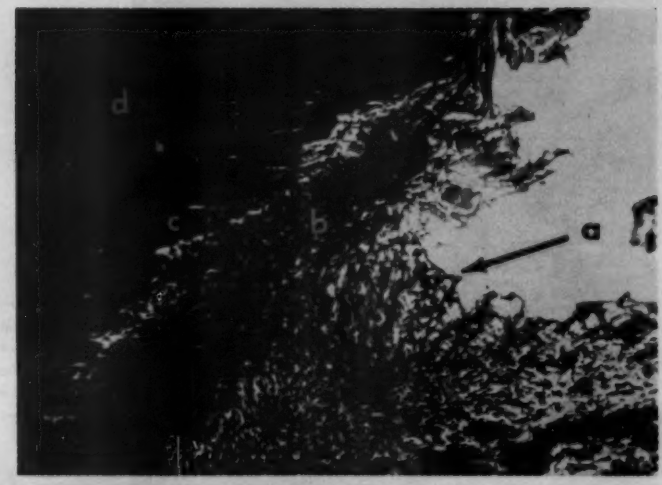

Fig. 1.—Filtration angle of the right eye in a tangential section. (*a*) The uveal part of the trabeculum; (*b*) the dense scleral part of the trabeculum; (*c*) canal of Schlemm; (*d*) the sclera, and (*e*) the root of the iris. Frozen section, Hortega method.

Fig. 2.—Filtration angle of the left eye in a tangential section. (*a*) The uveal part of the trabeculum; (*b*) the dense scleral part of the trabeculum; (*c*) Schlemm's canal filled with endothelial nuclei; (*d*) the sclera, and (*e*) the root of the iris. Frozen section, Hortega method.

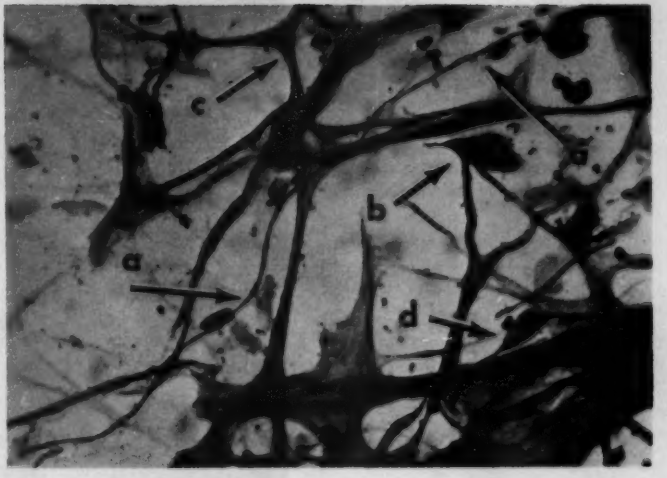

Fig. 3. — A normal-appearing nerve fiber (*a*) of the uveal part of the trabeculum. The loose meshwork of the uveal trabeculum (*c*) is visible. (*b*) Terminal swelling of an interrupted and degenerated nerve fiber; (*d*) local swelling of a continuous nerve fiber in the trabeculum. Frozen section, Hortega method.

Fig. 4.—Numerous nerve fibers in the trabeculum. (*a*) Nerve fibers with interruptions and an irregular caliber; (*b*) swollen nerve fiber; (*c*) advanced swelling of continuous nerve fiber. Frozen section, Hortega method.

Fig. 5.—Nerve fibers of the trabeculum one of which (*a*) shows advanced local swelling and disintegration. The other (*b*) is generally swollen. Frozen section, Hortega method.

Fig. 6.—Nerve fibers in the trabeculum, some of which (*a*) appear about normal. One fiber has become interrupted and shows an advanced bulb-like swelling (*b*). Frozen section, Hortega method.

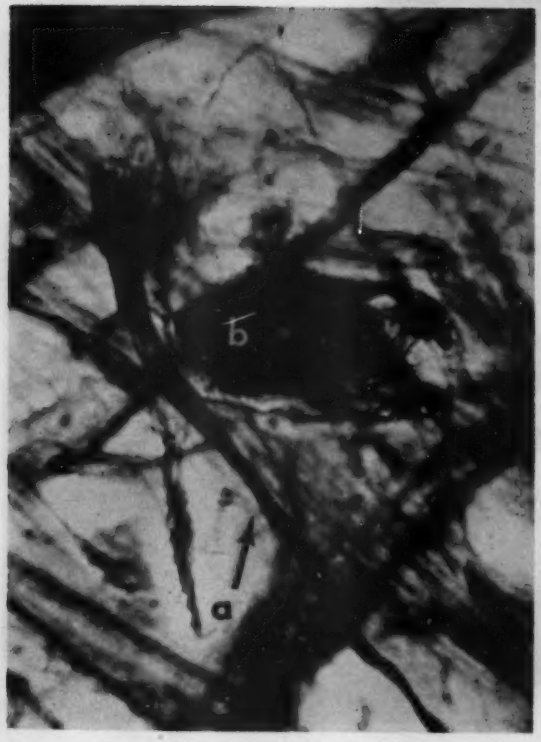

Fig. 7.—Degenerated nerve fibers in the trabeculum. One fiber (*a*) has become interrupted and forms a bizarre terminal swelling. The large body of swollen nerve substance (*b*) is all that remained of another nerve fiber. Frozen section, Hortega method.

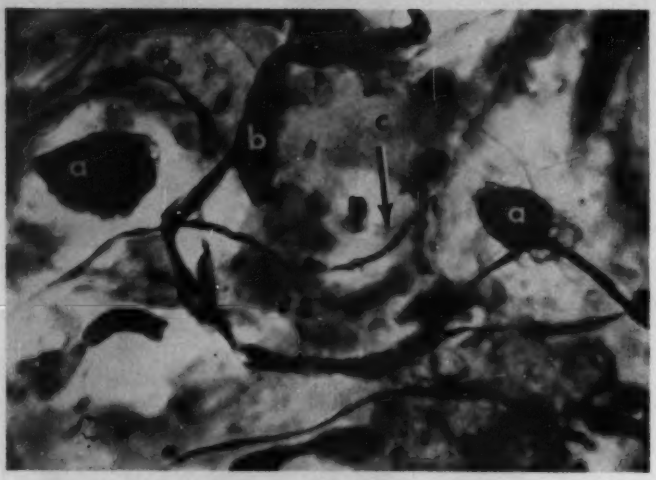

Fig. 8.—Large formations of the substance of degenerated nerve fibers (*a*), swollen interrupted nerve fibers (*b*), and normal appearing nerve fibers (*c*) in the trabeculum. Frozen section, Hortega method.

1 and 2). The normal meshwork-like architecture of the trabeculum was virtually lost. This was most advanced in the deep scleral parts of the trabeculum, while the uveal part of the trabeculum still showed its normal meshwork-like arrangement (Figs. 1 and 2).

Nerve fibers could be demonstrated in all parts of the trabeculum of both eyes. Figure 3 shows a good example of such a nerve fiber in the loose uveal part of the trabeculum of the right eye. On the picture the fiber appears to run free through the intertrabecular space. It must be pointed out, however, that it actually runs within the protoplasm of endothelial cells which in this instance bridge the trabecular space. The endothelium remained virtually unstained in this slide. Such normal-appearing nerve fibers were seen all through the trabeculum. However, most of the nerve fibers in the trabeculum of both eyes showed very advanced pathology. Figures 4 to 10 show different types and stages of the nerve fiber pathology found in the trabeculum of the two eyes of this patient. Figure 4 shows a number of fine nerve fibers in the trabeculum. One of these fibers shows fragmentation; another one shows a local swelling of

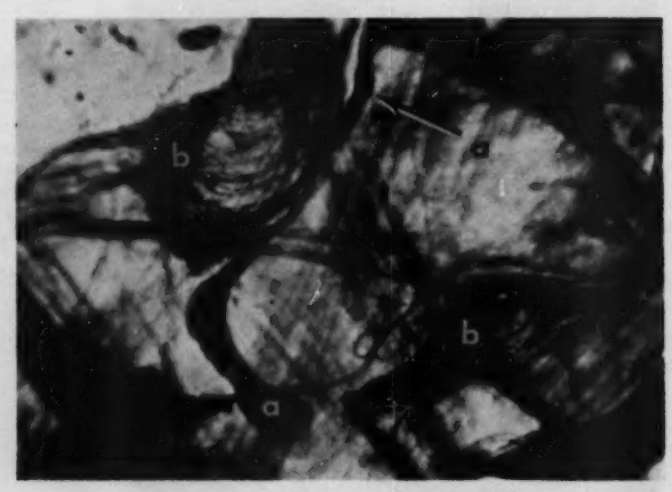

Fig. 9. — Swollen degenerated nerve fibers with large terminal formations at the site of their interruption (*a*) and large bizarre bodies of nerve fiber substance (*b*) in the trabeculum. Frozen section, Hortega method.

Fig. 10.—The scleral part of the trabecu'um shows small intertrabecular spaces (*a*) and thickened trabeculae (*b*). The nuclei of the proliferated endothelium are not very clearly visible in this picture. Frozen section, Hortega method.

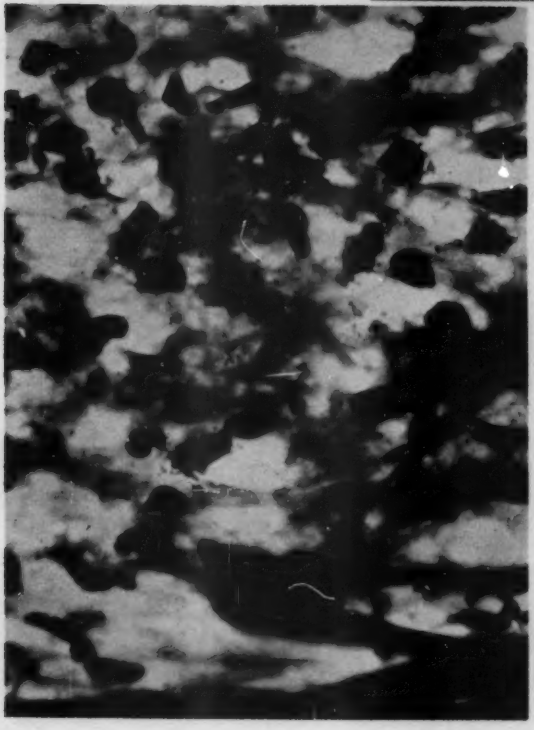

Fig. 11. — Proliferated endothelial cells in the canal of Schlemm. Pigment granules are seen among the cells and are often found within the endothelial protoplasm. Frozen section, Hortega method.

the neurite. Three other fibers in Figure 4 exhibit different stages of swelling. Figure 5 demonstrates a more advanced local swelling of a nerve fiber in the trabeculum. Interruption, fragmentation, and very advanced bulb-like swelling of a nerve fiber are seen in Figure 6. Figures 7 and 8 show large bizarre bodies of swollen nerve substance which developed from interrupted and degenerated neurites of the trabeculum. These bodies had remained in the trabeculum after the interconnecting nerve fibers had already become completely atrophic. The most advanced stage of nerve fiber swelling and degeneration found in the trabeculum of this case is seen in Figure 9. Large formations of swollen nerve substance were all that had remained of the delicate nerves which are normally found in the trabecular meshwork. The fact that all the nerve fibers of the trabeculum of both eyes of this case were swollen made it possible to stain and visualize all the nervous structures of the trabeculum in this case much better than that is normally possible. With all these nerve fibers stained and swollen I was very much impressed by the richness of nerve supply of the trabeculum.

Figure 10 shows that the increased density of the architecture of the scleral part of the trabeculum in these two eyes which was described above had resulted in an advanced narrowing of the intertrabecular spaces. This was caused in part by the increased thickness of the trabeculae themselves. However, there also was a definite proliferation of the endothelial cells of this area which added to the increase of the tissue mass (Fig. 10). The proliferation of the endothelial cells was even more extensive in the canal of Schlemm. The latter appeared virtually filled with endothelial cells (Fig. 11). The endothelium of these areas was not normal in shape and arrangement. The cells appeared rounded and not very well attached

Fig. 12.—The nerve fibers of the ciliary plexus. These fibers appear normal, and many nuclei of Schwann cells are seen among them. Frozen section, Hortega method.

Fig. 13.—A normal appearing nerve bundle and normal nerve fibers in the ciliary muscle. The nuclei of the ciliary muscle fibers are well visible. Frozen section, Hortega method.

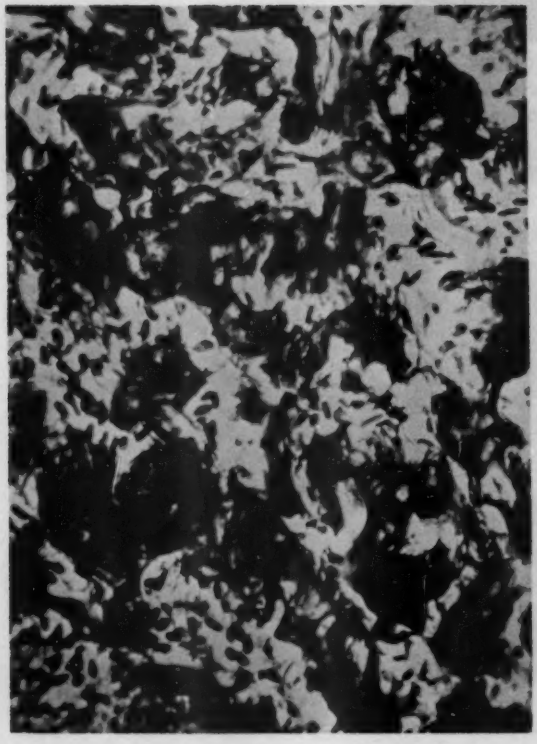

Fig. 14.—Fibrosis of the ciliary muscle. The nuclei of the ciliary muscle cells are seen between the bundles of fibrotic tissue, which are darkly stained in this section. Frozen section, Hortega method.

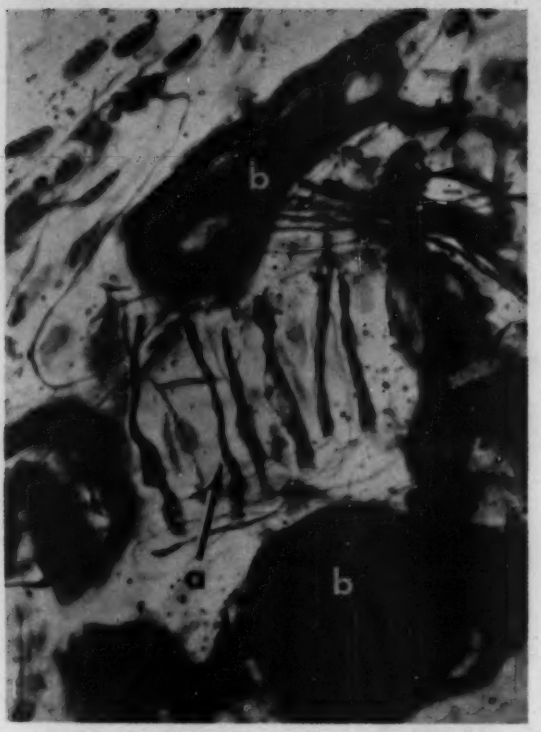

Fig. 15.—Nerve bundles and nerve fibers (*a*) between fibrotic areas (*b*) of the ciliary body. Frozen section, Hortega method.

to the trabecular framework. The connective tissue fiber bundles of the trabeculae were continuous and regular and showed no fragmentation.

It is important to emphasize that the severe nerve fiber pathology found in the eyes of this case was limited to the trabeculum. The ciliary plexus (Fig. 12) and the nerve fibers of the ciliary body (Fig. 13) were normal. The nerve fibers of the ciliary body were well stained in their course through the ciliary plexus and in their

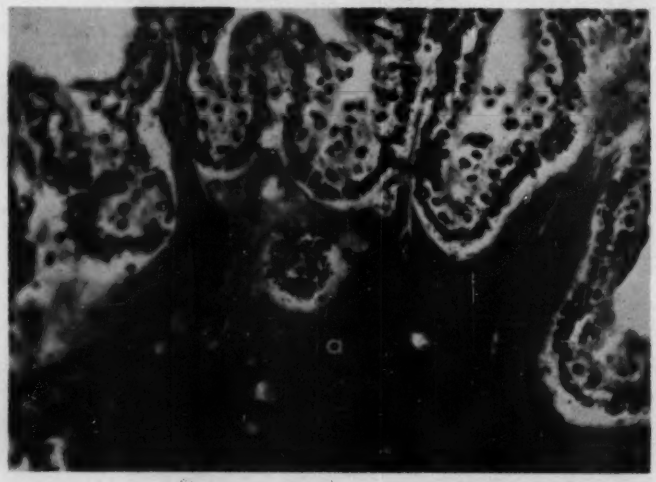

Fig. 16.—Ciliary processes with fibrosis and hyalinization of their stroma (*a*). The layers of the ciliary epithelium are seen in the upper part of the picture. Frozen section, Hortega method.

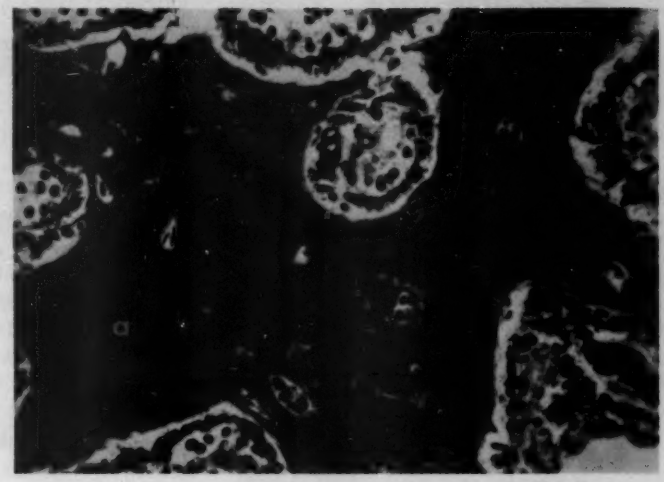

Fig. 17.—Area of dense fibrosis and hyalinization in the stroma of the ciliary processes (*a*). Frozen section, Hortega method.

branchings and endings at the nonstriated muscle fibers of the ciliary body and in the ciliary processes. There was, however, very extensive fibrosis of the ciliary muscle and the ciliary processes. Figure 14 shows a longitudinal section through the ciliary body of the right eye. All the dark-stained tissue represents dense bundles of connective tissue which has replaced atrophic smooth muscle fibers. The nuclei of the remaining muscle fibers are seen in the picture between the dark-stained fibrotic areas. The nerve bundles and fibers of the ciliary body appeared normal and undisturbed by this advanced fibrosis (Fig. 15). Fibrosis and hyalinization were found in many of the ciliary processes (Figs. 16 to 18). The fibrosis was in some areas very extensive and virtually replaced all the stroma of the processes (Figs. 16 and 17). Some processes, however, showed only very little fibrotic changes and appeared about normal (Fig. 18). The blood vessels were well preserved in all the ciliary processes, but they were mostly completely surrounded by dense hyalinized connective tissue (Fig. 18).

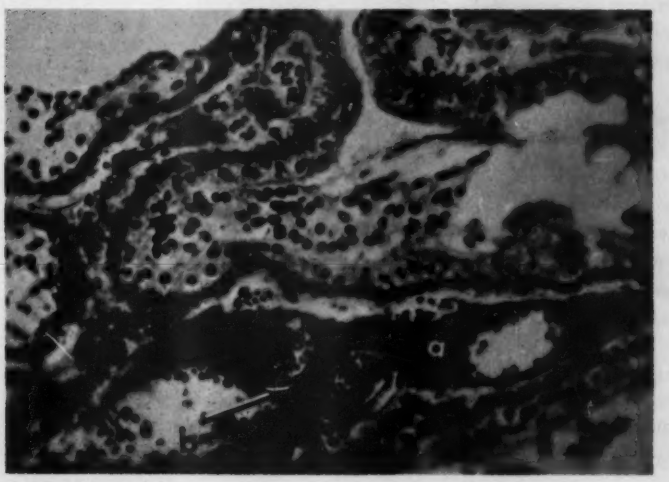

Fig. 18.—Ciliary processes which show virtually no fibrosis (upper part of picture). Some fibrosis (*a*) which surrounds blood vessels (*b*) is seen in the lower part of the picture. Frozen section, Hortega method.

Comment

Some of the findings in the trabeculum of the present case of open-angle glaucoma are a confirmation of the findings which were published on this subject by other authors. Teng, Paton, and Katzin[5] reported different types of degenerative changes in the trabeculum in primary open-angle glaucoma. These changes were proliferation of the endothelium, granularity of the collagen and degeneration of the elastic fibers of the trabeculae, hyalinization of the endothelium, and distortion and obstruction of the collector channels. Of these findings I observed in my case the proliferation of the endothelium which was most advanced in the deep parts of the scleral trabeculum and the canal of Schlemm. In my case the trabeculae showed extensive swelling, but there was no granularity or fragmentation of their collagen fibrils. In a recent study, Kornzweig, Feldstein, and Schneider[6] listed the following changes as typical findings in the trabeculum of cases with primary glaucoma: thickening and sclerosis of the trabeculae, narrowing or obliteration of the intertrabecular spaces, variation in the patency of the canal of Schlemm from narrowing and partial occlusion to complete occlusion, endothelial proliferation causing occlusion of Schlemm's canal, and pigment granules and cells in varying amounts in the intratrabecular spaces. My observations are a complete confirmation of all these listed changes found by Kornzweig, Feldstein, and Schneider.[6] In addition to the list of trabecular pathology in open-angle glaucoma given by these authors, I should like to mention that the thickening of the trabeculae and the proliferation of the endothelium was in this case much more advanced in the scleral part of the trabeculum than in the uveal part.

Zimmerman[7] has reported that acid mucopolysaccharides are normally found in the human trabeculum. He was observed that this substance is missing in the trabeculae of cases with endothelial atrophy in angle closure and other conditions (personal communication). It would be extremely interesting to know whether or not an increase of the mucopolysaccharides may be found along with the proliferation of the endothelial cells in open-angle glaucoma.

The observation of extensive pathology of the nerve fibers of the trabeculum of both eyes of this patient with well-documented open-angle glaucoma is the outstanding finding of this study. It is well known from the work of Holland, von Sallmann, and Collins[8,9] and from my own studies[10] that the normal human trabeculum is supplied by a dense system of delicate nerve fibers. These nerve fibers have their origin in the ciliary plexus, and their terminal branches end in the trabecular endothelium without forming special end structures.[10-12] The extensive pathology of the trabecular nerves in the two eyes of the present case are an important finding. However, we do not know yet what this finding means. The nerve changes in this case do not indicate whether they are the primary pathology or just part of the extensive secondary pathology found in open-angle glaucoma. From general neuropathology the type of nerve fiber pathology observed in the trabeculum of this case is known to occur in cases of extremely chronic and slowly progressive involvement. Any acute nerve fiber damage results in a destruction and total loss of the nerve fibers. The bizarre swellings and the other chronic changes of the nerve fibers in the trabeculum of this case therefore indicate that the involvement of the trabecular nerve fibers in open-angle glaucoma is of chronic and slowly progressive nature. It must be emphasized that this nerve fiber pathology was limited to the trabeculum and did not involve the nerves of the ciliary body. Much has to be learned about the changes of the trabecular nerves in other cases of open-angle glaucoma and in other conditions involving the trabeculum before conclusions can be drawn from the findings in the present case. I can state already that the cases of secondary angle-closure glaucoma which I recently reported[10] showed a total atrophy of all trabecular nerves.

It is a long-known fact that fibrosis and hyalinization of the ciliary body and the ciliary processes are usually found in any eyes of elderly patients. This fibrosis seems generally to be increasing with the age of a patient. However, there are exceptions to this rule. This fibrosis goes along with atrophy of the ciliary muscle and the normal stroma. In cases of absolute glaucoma or long-standing glaucoma we often find virtually all the normal stroma replaced by hyalinized fibrous tissue. The present case showed relatively little fibrosis and hyalinization of the ciliary muscle and of the ciliary processes. There still were many ciliary processes virtually without fibrosis and with very well-preserved and blood-filled blood vessels. The significance of the fibrotic changes in the ciliary processes in relation to the senile or glaucomatous changes in the trabeculum is not yet understood.

In concluding, I would like to state that this study is to be considered a preliminary report. Cases of open-angle glaucoma are difficult for the eye pathologist to obtain, and I hope that this report may stimulate interest for research in the same direction by anyone who might have the chance to study the eyes of similar cases.

Summary

The pathology and the neuropathology of the trabeculum and the ciliary body of both eyes of a clinically well-documented case of open-angle glaucoma are demonstrated. As far as the changes of the trabeculum and the trabecular endothelium are concerned the findings of earlier authors could be confirmed. The study of the nerves of the trabeculum revealed extensive nerve fiber pathology of a very chronic type which is considered an important and new finding.

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A Comparison of the Influence of Parenteral Trypsin, Cortisone, and Heparin on Acute Inflammation

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Reports have recently appeared in the literature concerning the effectiveness of parenterally administered trypsin in the suppression of inflammation in a variety of inflammatory and thrombotic diseases. Innerfield and his associates presented "clinical observations based on 6,456 trypsin infusions to 538 patients supporting the view that trypsin rapidly suppresses acute inflammation of diversified origin (bacterial, viral, allergic, and chemical)." [1] Specifically mentioned in this study were 12 cases of thrombosis of the central retinal vein which after trypsin therapy showed subsidence of retinal edema in 24 to 48 hours; 5 cases of acute iridocyclitis all showed dramatic improvement of symptoms. Hopen,[2] in a study devoted to acute ocular inflammatory and thrombotic disturbances, reported impressive results in 7 of 11 cases refractory to cortisone and stated, "trypsin initiates biochemical reactions which result in prompt and sustained subsidence of acute inflammation."

Taylor, Overman, and Wright,[3] as the result of an experimental study, concluded that neither large nor small amounts of trypsin intravenously have any therapeutic effect whatever on artifically induced intravascular thrombi. These authors did not believe that the use of trypsin in man was justified. A search of the literature revealed no controlled experimental observations on the effect of systemically administered trypsin on acute ocular inflammatory processes.

In order to evaluate trypsin adequately we planned to investigate its effect by comparing it with two other substances known to have a modifying effect on inflammatory processes, namely, heparin [4] and cortisone.[5] For this purpose, allergic reactions were produced in the eyes of albino rabbits. In previous experiments this reaction had been found a convenient and accurate biological method to assay the effect of various therapeutic agents.[4-7] Very slight changes in the intensity of the reaction are reflected by the degree of hyperemia and swelling of the iris, by the hyperemia and chemosis of the conjunctiva, by cloudiness of the aqueous humor, and by exudate in the anterior chamber. This paper reports the results of such a study.

Materials and Methods

Thirty-two albino rabbits, each weighing approximately 3.0 kg., were sensitized to horse serum in the following manner: Each animal was given intravenous injections of normal horse serum on the first day of 0.1 ml., on the second day of 0.3 ml., and on the third day of 0.5 ml. Five days after the last injection each animal was given another injection intravenously of 0.2 ml. of normal horse serum. Fifteen days after the last intravenous injection of horse serum, the dermal reactivity of each rabbit was determined by the intracutaneous injection into the shaved skin of the right upper flank of 0.1 ml. of a 1:10 dilution of horse serum in 0.85% soduim chloride solution. This injection was performed in each of two

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sites, 8 cm. apart. The reaction was observed at the end of 24 hours by measuring the diameter of the erythema and induration of each site. The average diameter of the two sites was determined. Two days later the animals were divided into four groups of eight animals each. Based on the skin reaction, each group contained animals of the same degree of hypersensitivity.

Technique of Anterior Chamber Injection. The technique used for the anterior chamber injection was as follows: the eyes were anesthetized topically with 1% tetracaine (Pontocaine) solution and proptosed. A sterile 27-gauge needle attached to a sterile tuberculin syringe was directed obliquely through the corneal stroma at the limbus for a distance of 3 mm. prior to entering the chamber; 0.1 ml. of sterile horse serum in the syringe was mixed with the primary aqueous by moving the plunger of the syringe in and out three times. The needle was withdrawn rapidly with 0.1 ml. of fluid remaining in the syringe. In this manner the initial volume of the anterior chamber was not altered. Since the average volume of the anterior chamber of the rabbit is 0.25 ml., a 40% solution of the material injected remained in the anterior chamber.

Drug Preparations Employed.—1. Trypsin: On the basis of reports in the literature,[1,2] we employed a dose of 10 mg. of crystalline trypsin suspended in sesame oil.* This material was given in two injections of 5 mg. each, 12 hours apart.

2. Cortisone: The dose of cortisone † was 10 mg. per rabbit, given in two injections of 5 mg. each, 12 hours apart. This dose had been found in previous studies to inhibit ocular inflammation.[5]

3. Heparin: In a previous study we had found that 17 mg. of sodium heparin solution per kilogram given intravenously every 6 hours over a 24-hour period had an inhibitory effect on ocular inflammation. In that study the average total dose was 210 mg. of soluble sodium Heparin per animal. In the present experiment Depo-heparin ‡ (solution of heparin in gelatin and dextrose) was employed, since it had been shown by others that heparin used in this form was effective in inhibiting inflammation.[8]

Experimental Groups

GROUP I (Untreated Controls).—Both eyes of each control animal were given injections of horse serum in the manner described above.

GROUP II (Trypsin-Treated).—Both eyes of each animal were administered injections of horse serum in the manner described above. Immediately after the anterior chamber injection, each animal was given an injection intramuscularly with 5 mg. of trypsin suspended in 1.0 ml. of sesame oil. An additional injection of 5 mg. of trypsin was given 12 hours later.

GROUP III (Cortisone-Treated).—Both eyes of each animal were administered injections of horse serum in the manner described above. Immediately after the anterior chamber injection, a subcutaneous dose of 5 mg. of cortisone was given. An additional subcutaneous injection of 5 mg. of cortisone was given 12 hours later.

GROUP IV (Heparin-Treated). — Both eyes of each animal were given injections of horse serum in the manner described above. Immediately after the anterior chamber injection, the animals were given injections with 200 mg. of Depo-Heparin into the muscle of the right thigh. Twelve hours later a second injection of 200 mg. of Depo-Heparin was given subcutaneously.

Results

The eyes of the four groups of animals were examined at 4, 8, 12, and 24 hours after the anterior chamber injection. The observer evaluating the degree of reaction in the eyes (M. W. B.) was unaware of the drug used in any individual animal at the time of the eye examination. Thus the read-

* The trypsin used in this study was supplied by the National Drug Company and is marketed under the trade name Parenzyme.

† The cortisone used in this experiment was supplied by Merck & Co., Inc.

‡ The Depo-Heparin was supplied by the Upjohn Company.

ings were entirely unbiased. The eyes were graded by degree of reaction of the conjunctiva, anterior chamber, and iris. A numerical value was given according to the degree of reaction observed. A reaction was graded 3 if it were severe, 2 if moderate, and 1 if mild. The conjunctival reaction was graded on the basis of chemosis, hyperemia, and discharge. The anterior chamber reaction was graded on the basis of cloudiness and exudate, and the iris reaction was graded on the basis of the amount of hyperemia and thickening. A maximal reaction would total 9.

At each period of observation the total numerical value of the reaction of the eyes of each group of rabbits was determined and then divided by the number representing the maximal reaction possible for eight rabbits. This figure multiplied by 100 gave the per cent maximal reaction possible. The results are shown graphically in Figure 1.

GROUP I (Untreated Controls).—A violent inflammatory reaction appeared which reached its maximum intensity four hours after the anterior chamber injection of horse serum. There was a slight reduction in the intensity of the reaction at the 24-hour observation period.

GROUP II (Trypsin-Treated Animals.)—The inflammatory reaction in this group was essentially the same as in the control group. The reaction became severer than that of the controls at the eight-hour observation period. In all subsequent observations the degree of inflammation in this group was as severe as that in the control group.

GROUP III (Cortisone-Treated Animals).

The reaction observed at four hours was essentially the same as that observed in the controls. At the 8-hour period the reaction had subsided slightly, and at the 12-hour period the inflammation had begun to subside more rapidly than that seen in the control group. This trend was more pronounced at the end of 24 hours, at which time the controls showed 65% of maximal reaction possible, while cortisone-treated group showed 35% of maximal possible reaction.

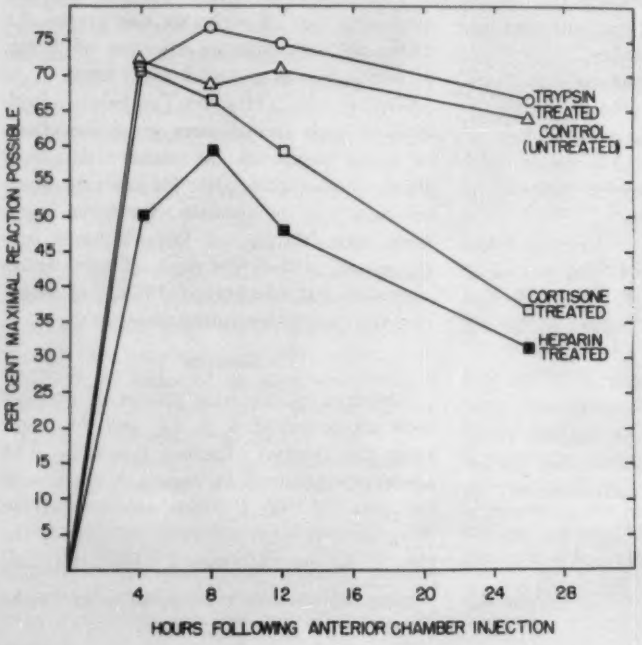

Fig. 1. — Influence of parenteral trypsin, cortisone, and heparin on acute ocular inflammation.

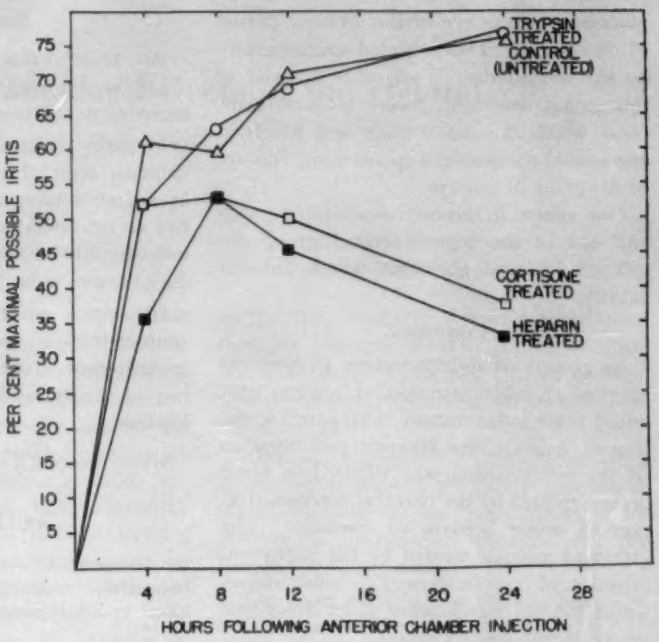

Fig. 2. — Influence of parenteral trypsin, cortisone, and heparin on acute iritis.

GROUP IV (Heparin-Treated Animals.)— The inflammatory response in the heparinized animals was less than in the other groups. The progression of the inflammation was delayed, and the maximal reaction was less than that observed in the control, trypsin-treated, or cortisone-treated groups.

Comparison of Iritis

The eye reaction charted in Figure 1 represents an average of the total individual readings of the conjunctiva, anterior chamber, and iris. We examined the severity of the iritis alone in order to compare the effect of the various drugs on iris hyperemia and edema. These results are shown in Figure 2.

At eight hours the degree of iritis in both the heparinized and cortisone-treated animals had reached 52% of the maximal reaction possible. Subsequently there was rapid subsidence of iritis in both groups to 35% at 24 hours. This is in contrast to the greater degree of iritis shown by both the control and the trypsin-treated groups. At the 24-hour period, while the iritis of the heparin- and cortisone-treated groups was rapidly subsiding, the iritis of the trypsin-treated and control groups had exceeded 75% of the maximal reaction possible and was still increasing.

Incidence of Glaucoma

The animals were observed for two days after the 24-hour reading, and the incidence of glaucoma was noted (Table). One animal in the control group showed a transient glaucoma in one eye at 24 hours which spontaneously subsided on the second day.

In the trypsin-treated group of animals one was observed to have mild transient

Incidence of Glaucoma

Group	No. Rabbits Involved	No. Eyes Involved
Control	1	1
Trypsin	3	5*
Cortisone	1	2
Heparin	1	2

* One eye spontaneously ruptured after 48 hr.

glaucoma in one eye at the 24-hour period of observation. This subsided spontaneously by the second day. Two other animals in this group developed severe bilateral glaucoma which did not subside and which in one animal resulted in a spontaneous rupture of the globe of one eye.

One animal in the cortisone-treated group and one in the heparin-treated group developed bilateral glaucoma which did not subside.

Comment

In groups of hypersensitive animals the anterior chamber injection of antigen produced acute inflammation. Compared to the control animals, the severity and duration of the inflammation was reduced in those groups treated by the parenteral administration of either heparin or cortisone. The group of animals treated by the parenteral injection of trypsin showed an inflammation which did not significantly differ from that shown by the control group.

In this study we were unable to substantiate, under controlled experimental conditions, the clinical observations of Innerfield [1] and Hopen,[2] i. e., that trypsin rapidly suppresses acute inflammation.

In a consideration of the data obtained on the inflammation shown by the iris alone, a dramatic reduction in the degree of hyperemia and edema of the iris was observed in the groups treated with cortisone or heparin. While the severity of iritis in these groups was subsiding the iritis in the control and trypsin-treated groups was increasing (Fig. 2).

Although statements have been made that the parenteral use of trypsin resulted in improvement of symptoms of glaucoma,[1,2] we observed as high an incidence of secondary glaucoma in the group of experimental animals treated with trypsin as in the other groups.

Summary

An acute ocular inflammation was produced in hypersensitive rabbits by the anterior chamber injection of antigen.

Heparin or cortisone administered parenterally reduced the intensity and duration of ocular inflammation. Parenteral trypsin had no inhibitory effect on the development, intensity, or duration of experimentally produced acute ocular inflammation.

Glaucoma occurred as frequently in animals treated parenterally with trypsin as in untreated control animals or in those treated parenterally with either cortisone or heparin.

Wilmer Institute, The Johns Hopkins Hospital (5).

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Studies on Intraocular Effects of the Orbital Parasympathetics

II. Effect on Intraocular Pressure

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It has been reported in a preceding publication [1] that in previously sympathectomized cats, when the connections of the ciliary ganglion to the inferior oblique and the inferior rectus muscles and to the unstriated retrobulbar muscle mass were severed, a controlled electric stimulus applied to the orbital parasympathetic pathway by means of a bipolar electrode produced a uniform response of the intraocular pressure in the stimulated eye. This was predictable with the highest degree of confidence. The response was characteristically a reduction in intraocular pressure.

The characteristics of this pressure response as well as the effect of various extraocular factors and of variation in stimulus characteristics were studied in 140 eyes. The results of this investigation are the subject of this communication.

The preparation as well as the equipment and techniques employed in these studies were described in the previous publication.[1]

Effect of Parasympathetic Stimulation on Intraocular Pressure

The characteristics of the intraocular pressure response will be described in three stages: the immediate response to stimulation, the pressure behavior during stimulation maintained for varying periods of time, and the pressure behavior on cessation of the stimulus.

Pressure Response to Stimulation.—On electric stimulation of the ciliary ganglion in the anesthetized cat, an immediate rapid reduction in intraocular pressure on the stimulated side ensued.

The onset of reduction became detectable 0.1-0.2 seconds after the beginning of stimulation. The reduction then proceeded at a very rapid rate to reach a maximum in 1-2 seconds (Figs. 1, 2, and 3). The magnitude of this reduction for the average working stimulus (3-5 volts, f=10−40 cps, delay 1 ms., duration 1-10 ms.) ranged between 3 and 5 mm. Hg for initial intraocular pressure levels of 15-20 mm. Hg; this response occurred without a single exception in 3,500 trials on 133 eyes. In the remaining seven eyes, stimulation produced the parasympathetic effect on the pupil and lens,[1] but failed to produce the intraocular pressure response. In these eyes the initial intraocular pressure varied between 9 and 12 mm. Hg at the time of stimulation. In two of these eyes the pressure response was later obtained after the intraocular pressure had risen spontaneously during the experiment to 15 mm. Hg. The importance of this observation will be elaborated in a future publication.

The magnitude of the pressure reduction in the same preparation and with the same initial intraocular pressure varied directly with the stimulus intensity and with the

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Department of Ophthalmology, State University of Iowa, University Hospitals.

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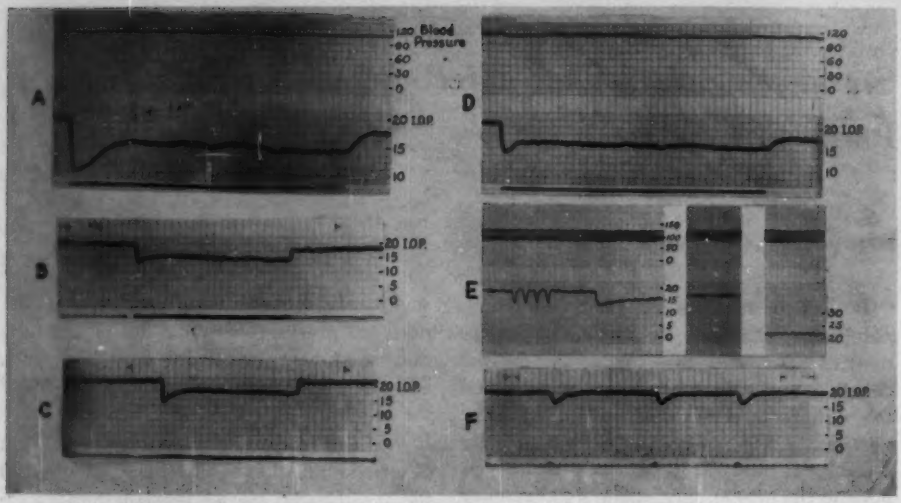
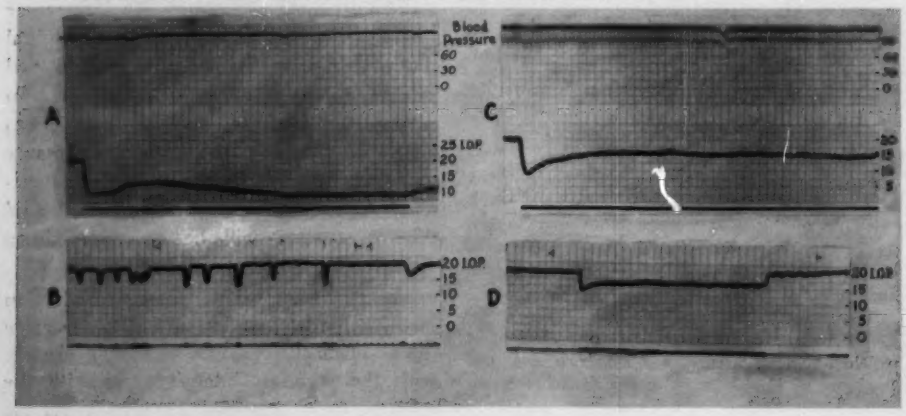


Fig. 1.—Intraocular pressure response to electrical stimulation of the orbital parasympathetic pathway. The solid line records the duration of stimulation superimposed on a one-second timer. *A* and *D*, upper tracings: records of average systemic arterial pressure simultaneous with lower tracings: records of intraocular pressure of the stimulated eye in millimeters Hg before, during, and after 13 minutes of stimulation. *B* and *C*, records of intraocular pressure response to seven minutes of stimulation. *E*, arterial and intraocular pressure are simultaneously recorded. Stimulus duration of 1 second repeated every 10 seconds produced the first four responses. Maintained stimulation for 25 minutes produced the fifth response from which a record of the 1st, the 13th, and the 25th minutes of maintained stimulation is shown. Note that the steady-state pressure during maintained stimulation is higher than the pressure before stimulation. *F*, intraocular pressure response to a duration of 0.3 seconds.

duration of the pulse. An additional reduction of 1-3 mm. of Hg could be obtained either by increasing the intensity from 5-10 volts or by increasing the pulse duration from 1-10 ms. or both (Fig. 2*B*). Various changes in the stimulus characteristics failed

Fig. 2.—Intraocular pressure response to electrical stimulation of the orbital parasympathetic pathway. *A* and *C*, upper tracings: records of systemic arterial pressure simultaneous with lower tracings: records of intraocular pressure in millimeters Hg showing response to 15 minutes of stimulation. *B*, record of intraocular pressure showing effect of changing the duration of the pulse from 1 msec. (smaller responses) to 10 msec. (larger responses) and that this effect is independent of sequence. Duration of stimulation varied from 0.5 to 3 seconds. *D*, response of intraocular pressure to eight minutes of stimulation.



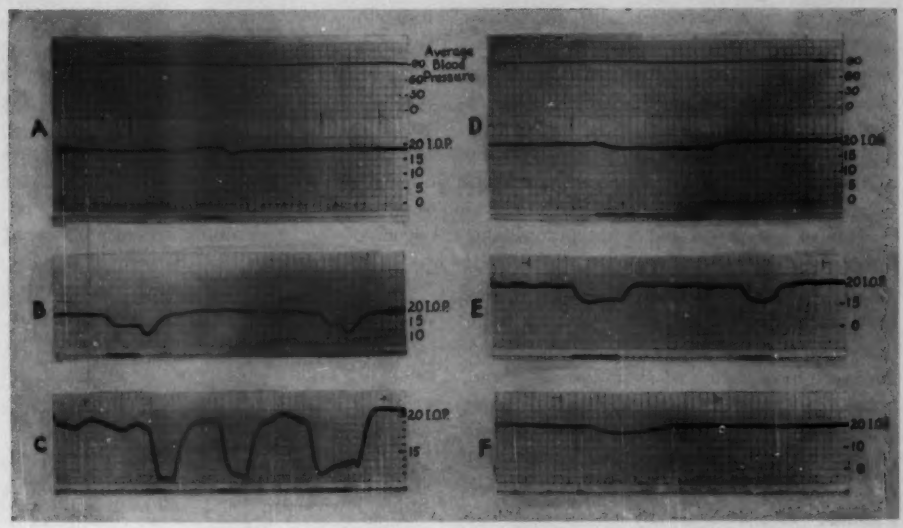


Fig. 3.—Response of intraocular pressure to stimulation of the orbital parasympathetic pathway. *A*, intraocular pressure response to stimulation when the connection of the ciliary ganglion to the orbital smooth muscles and to the inferior rectus were intact and *D*, after these connections had been severed in the same preparation. *B* shows the appearance of a post-stimulus "dip" when stimulation was associated with visible contraction of the extraocular muscles, and *E* shows its disappearance when the position of the electrode was changed eliminating electrical leak. *C* shows a slight poststimulus dip not associated with visible signs of effective electrical leak and that disappeared in *F* after the position of the active electrode had been changed.

to alter the quality of the response or the character of its onset.

Pressure Behavior During Stimulation.—The following types of pressure behavior were obtained during maintained stimulation. They are listed in their order of frequency.

1. The pressure level attained at maximum reduction was maintained throughout the period of stimulation.

2. After maximum reduction was attained, the pressure rose gradually to a new level which was, nevertheless, 2-3 mm. Hg lower than prestimulus level and which was maintained throughout the period of stimulation.

3. The pressure behavior described in 1 and 2 was followed after 5-10 minutes of maintained stimulation by a slow progressive reduction so that the level attained at the end of prolonged stimulation was 1-3 mm. Hg lower than what it was initially at maximum reduction.

4. The pressure continued to rise after maximum reduction until the prestimulus level was reached; this level was then maintained throughout the period of stimulation.

5. On rare occasions the rise described in 4. would continue until a pressure level 1-2 mm. Hg higher than the prestimulus level was reached and maintained throughout the stimulation.

The entire variety of pressure responses was obtained without any associated changes in systemic arterial pressure which was recorded simultaneously. On occasions arterial pressure changes were observed on intense stimulation; however, irrespective of whether the arterial pressure change was a rise or a reduction, the intraocular pressure response was always a reduction on stimulation.

It is proper to mention at this stage that when maintained stimulation produced Type 4 or Type 5 behavior, an increase in the intensity of the stimulus was, in general,

successful in converting these into either of the first three types. There was no detectable factor or factors with which the occurrence of these various types of behavior could be correlated. In general, Types 1, 2, and 3 of pressure behavior occurred during maintained stimulation. The occasional occurrence of Type 4 or 5 in certain preparations was not associated with a detectable difference in conditions from those that existed when Types 1, 2, and 3 were obtained in the same preparation.

Pressure Behavior on Cessation of Stimulation.—On cessation of short-lasting stimulation (less than one minute), the following types of pressure behavior were observed:

1. A quick rise in pressure occurred and reached a maximum level in one to three seconds. This rise usually ended once the prestimulus pressure level was reached. Occasionally, however, a slight overshoot of 1 mm. Hg beyond the prestimulus pressure was observed which lasted two to five seconds.

2. Occasionally a dip of 0.25-0.50 mm. Hg occurred upon cessation of stimulation and lasted for one to two seconds, to be followed by either one of the two types of rise mentioned under 1. This slight reduction was not associated with the presence of signs of "electrical leak" during stimulation nor was it modified by altering the characteristics of the stimulus. It could be eliminated by altering the position of the active electrode (Fig. 3). The rarity of its occurrence rendered impossible any controlled evaluation of its causation.

On cessation of stimulation that lasted longer than five minutes, the following *additional* types of pressure behavior were noted and will be listed in their order of frequency.

A. When the pressure behavior had followed Types 1, and 2, or 3 during maintained stimulation, the most frequent types of behavior on cessation were as follows:

1. The pressure rose to a level 1-4 mm. lower than the prestimulus pressure; this level was maintained for 10-20 minutes before the eye recovered the prestimulus pressure.

2. A rise in pressure occurred and was similar to that observed in Type 1 on cessation of short-lasting stimulation.

3. The reduced pressure level maintained during stimulation remained the same on cessation of the stimulus. In general, recovery of the prestimulus pressure followed 30-40 minutes later.

B. When the pressure during maintained stimulation followed Type 4 or 5 behavior, cessation of stimulation produced the following type of behavior:

1. A rise in pressure which was less in magnitude than the reduction at the onset despite the fact that it occurred at a higher initial pressure level. Recovery of the prestimulus pressure level followed and was complete, in general, within five minutes.

2. No change in pressure level followed cessation of stimulation.

Association of Responses

In general, stimulation produced simultaneously all of the responses previously enumerated for the iris and lens,[1] as well as for the intraocular pressure. However, the intraocular pressure response was obtained when stimulation was applied after the pupil had become widely dilated by sectioning the central connection of the preganglionic trunk of the ciliary ganglion as well, as after the pupil had been constricted to a vertical slit with pilocarpine. At the same time no direct correlation was found between the magnitudes of the pressure reduction and the constriction of the pupil.

Furthermore, it has already been mentioned that in seven eyes maximum effects on the pupil and lens were obtained on stimulation without any accompanying intraocular pressure change.

Effect of Extraocular Orbital Factors on Response

In an attempt to investigate whether the intraocular pressure response to stimulation of the ciliary ganglion was a manifestation

of an intraocular or an extraocular event produced by parasympathetic stimulation or to an associated effect of electrical stimulation on the orbital muscles and vessels, various technical as well as pharmacologic procedures were used aimed at elucidating this question.

The effect of various pharmacologic agents on the response confirmed the results of the various technical procedures and will be reported separately.

Effect of Various Components of the Pathway.—The intraocular pressure response as well as the responses of the iris and lens were identical regardless of whether the electrode was applied to the ciliary ganglion, to the preganglionic trunk, or to either of the two postganglionic trunks. They remained the same, irrespective of whether the central connection of the preganglionic trunk to the third nerve were intact or completely severed.

All responses to stimulation were eliminated by interrupting surgically the continuity of the pathway anywhere between the site of application of the electrode and the point of entry of both postganglionic trunks into the globe. Sectioning only one of the two postganglionic trunks caused a reduction in the response, and, for apparent reasons, both had to be sectioned in order to interrupt the continuity of the pathway at this point and eliminate completely the response to stimulation of a more proximal site of the pathway.

The response of the iris, lens, and intraocular pressure to electric stimulation of the ciliary ganglion was also obtained when the ganglion was mechanically stimulated by holding it under firm pressure with the tip of a fine forceps.

Effect of Orbital Muscles.—The response was not modified in any manner after all the extraocular striated muscles had been sectioned at the proximal one-third of their bellies.

The possible effect of the "unstriated" orbital muscles was of special interest, since their tonicity influences the intraocular pressure and a possible relaxation of these muscles on parasympathetic stimulation might account for the intraocular pressure response. These muscles comprise essentially the retrobulbar muscle mass, arranged in bundles between the apex of the orbit and the posterior pole of the globe; the nictitating membrane and its muscle, which encircles the nasal one-third of the anterior half of the globe and intimately relates to the globe, and, finally, smooth muscle elements attached to both lids. It is to be recalled that in the final preparation,[1] the uniformity of the response was achieved after all connections of the parasympathetic pathway to extraocular structures including those extending from the ciliary ganglion to the unstriated retrobulbar muscle were severed.

Of particular interest in this regard was the role of the nictitating membrane and its muscle in the production of an intraocular pressure response to stimulation of the superior cervical ganglion. Such stimulation in an appropriate preparation produced dilatation of the pupil, retraction of the nictitating membrane, and a rise in intraocular pressure of 5-7 mm. Hg.

This pressure response was either completely eliminated or reduced to 0.5 or 1 mm. Hg when the same stimulation followed a complete excision of the nictitating membrane and its muscle (Fig. 5). However, this maneuver did not influence the intraocular pressure response to stimulation of the ciliary ganglion in any noticeable manner, nor was this response modified by complete excision of the entire retrobulbar muscle mass and of both upper and lower lids.

Effect of Other Orbital Structures.—Once the effect of the extraocular muscles, striated and unstriated was ruled out, it became important to investigate the role of a possible effect of electric stimulation on adjacent orbital blood vessels on the production of the intraocular pressure response.

The isolated parasympathetic pathway could be pulled laterally away from all

orbital structures and suspended in air by the electrode tip. When this space was more effectively isolated from the rest of the orbit by surrounding the entire pathway and electrode with wax paper or by filling this cavity with liquid paraffin, the intraocular pressure response remained unmodified. These maneuvers proved effective in raising the intensity of stimulation required to produce "effective electrical leak" by several-fold.

It was concluded from these results that the intraocular pressure response to stimulation of the parasympathetic pathway was not produced wholly or in part by the possible effect of such stimulation on systemic arterial pressure, on extraocular muscles or on orbital vessels, and that the response had to be accounted for exclusively by an intraocular event produced by such stimulation.

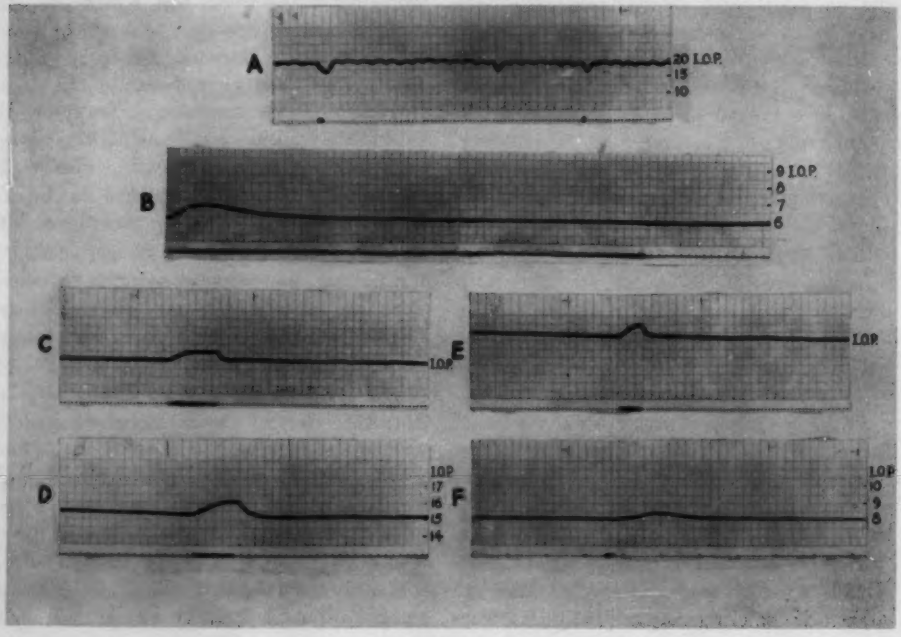
Effect of Death on Response

Once the response was obtained in the living anesthetized cat, the electrode was left in place and the set-up kept constant. Cessation of respiration and circulation was rapidly effected by an intracardiac injection of 50 to 100 cc. of air, by an intracardiac lethal dose of pentobarbital(Nembutal), or by exsanguination.

Effective stimulation at this stage always produced a rise in intraocular pressure instead of a reduction. This continued to be the response to stimulation irrespective of how high the initial pressure was made experimentally by injecting saline into the anterior chamber.

The same reversal occurred after enucleation (Fig. 2) confirming the results of Purnell et al.,[2] as well as after tying a strong ligature, in the living cat, strangulating all the structures emerging from the orbital apex.

Fig. 4.—Effect of death on the intraocular pressure response to electrical stimulation of the orbital parasympathetic pathway. The intraocular pressure response to stimulation, *A*, in the living anesthetized cat; *B*, after a lethal intracardiac injection of 50 cc. of air; *C*, after a lethal dose of pentobarbital (Nembutal); *D*, *E*, and *F*, in the enucleated eye.



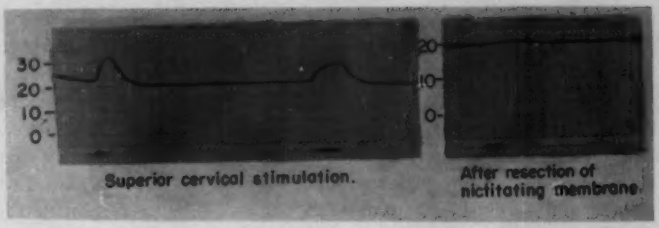


Fig. 5.—Record of intraocular pressure showing the effect of stimulation of the superior cervical ganglion of the same side when the nictitating membrane and its muscle are intact and the effect of the same stimulation applied after complete resection of the nictitating membrane and its muscle.

The magnitude of this rise was 0.5 to 1 mm. Hg. It seemed to carry an inverse relationship to the magnitude of the initial pressure.

Maintained stimulation failed to maintain the initial rise in pressure for more than 5-10 seconds; it was followed by a progressive reduction.

Interpretation of Results

Two components in the pressure response stand out as requiring two separate mechanisms: the immediate and the maintained reduction.

The immediate reduction requires rapid reversible changes in the volume of intraocular contents. The aqueous and vitreous compartments as well as the lens drop out of consideration. There remain the intraocular muscles and the vascular bed. Of the muscles, the ciliary and the iris sphincter reacted to stimulation; the behavior of the latter was not correlated with the response.

Contraction of the ciliary muscle produces two effects relevant to this problem: a reduction in muscle volume favoring a pressure reduction and a reduction in the diameter of the ciliary circle reducing the size of the effective shell containing the intraocular fluid and favoring a pressure rise. The response in the enucleated eye showed that the effect of the second component was predominant.

If the muscular contribution is the same in the living cat, then it can not account for the response and would have to be opposed by a simultaneous pressure-reducing mechanism capable of producing a net effect of reduction.

The effect of stimulation on the vascular bed may be either a direct one on the musculature of the vessels or an indirect one through ciliary muscle contraction. A direct effect, if it existed and was similar to the parasympathetic effect on the systemic circulation, should produce an increase in volume and pressure. On the other hand, the indirect effect would lead to a reduction of the volume of the vascular bed of the ciliary muscle and iris by the rapid emptying of the venous bed of the muscle and the reduction of the caliber of the ciliary arteries coursing through the muscle to form the major circle of the iris by active compression during contraction causing marked reduction in the filling pressure head of that vascular bed.

The cessation of pulsation in the arteries of the major circle on stimulation and the reduced pulse volume during maintained stimulation,[1] together with the reversal of the response on strangulation of the ocular circulation, favors strongly the interpretation that a reduction in the volume of the intraocular vascular bed is the pressure-reducing mechanism that can account for the net reduction response to stimulation in the anesthetized cat.

A more detailed investigation of the muscular and vascular component was undertaken under conditions of controlled variations in the arterial as well as the venous pressure, the intraocular pressure, and the ciliary muscle tone, in an attempt at separating these two antagonistic components of the response to stimulation. The results of this part of the studies supported the above-mentioned interpretation and will be reported in detail separately.

The behavior of the intraocular pressure *during maintained stimulation* is not explained by a mechanism producing only a reduction of a fixed magnitude in the volume of intraocular contents. For, then, a progressive rise would follow maximum reduction until the prestimulus pressure level was attained and would be maintained throughout the period of stimulation irrespective of the duration. This, however, was shown to be the unusual and rare behavior. Instead, the intraocular pressure during stimulation could be made to maintain a pressure level significantly different from the prestimulus level.

This indicates that stimulation must have effected, in addition, a change in one or more of the factors determining the level of intraocular pressure to be maintained by an eye. For all practical consideration, and in the absence of change in the systemic arterial pressure on stimulation, these factors are the inflow rate of aqueous, the resistance to outflow, and the pressure in the collector channels.

The effect of stimulation on the resistance to outflow and the possible role of the pressure in the collector channels were investigated and will be the subject of future publication.

The pressure behavior on cessation of long-lasting stimulation demonstrated a change in pressure equal to and in the opposite direction to that produced by stimulation. However, the absence of change, on occasions, on cessation of prolonged stimulation and the relatively reduced magnitude of the rise even when it occurred at higher intraocular pressures seem to indicate a decay of the immediate response or a compensation of its pressure-reducing component during prolonged stimulation. This was not always associated with detectable reduction in the pupillary and lens responses during the same period of stimulation.

Summary

Electrical stimulation of the isolated orbital parasympathetic pathway in the anesthetized cat produced an immediate reduction in intraocular pressure, which was maintained during prolonged stimulation. Death and strangulation of the ocular circulation reversed the response from a reduction to a slight rise in pressure.

Extraocular factors were ruled out as being responsible for this response.

Two components of the response require different mechanisms of production: the immediate and the maintained reduction in pressure.

Analysis of possible intraocular mechanisms led to the following interpretation for the immediate reduction: The muscular contribution to the response produced a net effect of a rise in pressure due to a reduction in the ciliary circle reducing the size of the effective shell containing the intraocular fluids. The pressure reduction was due to a simultaneous reduction in the volume of the vascular bed of the ciliary muscle and iris through the effect of contraction of the ciliary muscle on the vessels coursing through it to form the major circle of the iris.

The fact that the eye maintained a pressure lower than the prestimulus pressure during maintained stimulation of 5 to 45 minutes indicated that stimulation must have produced, in addition, a reduction in one or more of the following parameters: inflow rate of aqueous, resistance to outflow, and pressure in the collector channels, or a complex effect on these parameters resulting, in general, in a reduced intraocular pressure level.

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Experimental Aberrant Lipogenesis

VI. Biochemical Characterization of the Sudanophilic Material Produced

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Aberrant lipogenesis is a phenomenon which has been described by Cogan and Kuwabara in the first four articles of the present series.[1-4] The term "aberrant lipogenesis" refers to the formation of fat by tissues or cells which do not ordinarily form fat. Although later shown to be a very general phenomenon, aberrant lipogenesis was first described in the rabbit cornea. Since that tissue has been used in the present experiments, corneal lipogenesis will be described more fully.

Sections or "buttons" were cut from fresh rabbit corneas and placed in a medium of serum and sodium oleate (2 mg. per milliliter). The buttons were incubated at 37 C for varying lengths of time and then sectioned in the frozen state and stained with hematoxylin Sudan. Sudan-positive droplets were then found to be present in both epithelial and stromal cells. When incubation periods as long as 48 hours were used, the droplets were so large and so numerous that they greatly distended the cells. For other characteristics of this phenomenon, the previous papers in this series should be consulted.

Pirie and van Heyningen[5] have pointed out the importance of identifying the lipogenetic lipid by chemical analytic techniques. That was the purpose of the present study.

For simplicity a few definitions are in order. "Lipogenesis" as used here refers to the esterification of glycerol by fatty acids. It does not refer to the synthesis of fatty acids, as it is frequently used in the biochemical literature. "Esterified glycerol" refers to glycerol that is released from a bound form by alkaline hydrolysis and includes the glycerol of neutral fats and phospholipids.

"Esterified fatty acids" refers to fatty acids released from a bound form by alkaline hydrolysis and includes fatty acids derived from neutral fats, phospholipids, and cholesterol esters.

Materials and Methods

The technique of Cogan and Kuwabara outlined above for the demonstration of aberrant lipogenesis in rabbit corneas was used. The incubation period was 48 hours. After incubation, the corneas were washed free of excess medium with sodium chloride solution and were extracted with a chloroform-methanol mixture. Determinations of esterified glycerol, esterified fatty acid, phospholipid, and cholesterol concentrations were made.

As the procedures for the determination of concentrations of esterified glycerol and esterified fatty acid are new they will be described more fully. Two-thirds of the aliquots for these determinations were saponified, and one-third were not. Concentrations of glycerol and fatty acid were determined colorimetrically on all aliquots. Values for esterified glycerol and esterified fatty acid were differences between the respective concentrations of glycerol or fatty acid as found in saponified versus unsaponified aliquots.

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Public Health Research Fellow of the National Institute of Neurological Diseases and Blindness, Grant BF-7484 (Dr. Ciccarelli).

Comparison was made with previous experiments by histologic preparation of control corneal buttons.

Blood serum and eyes were obtained from young adult albino rabbits. Sodium iodoacetate (see "Results"), when present in the incubation medium, was at a concentration of 5×10^{-3}M. Buttons were extracted according to the method of Folch.[6] Saponification was carried out on samples intended for glycerol and fatty acid analysis according to the method of Van Handel and Zilversmit.[7] Doucil (a zeolite) was not used. Glycerol was determined by the method of Lambert and Neish [8] as modified by Van Handel and Zilversmit,[7] solutions of glycerol being used as standards. Fatty acid concentrations were determined by the method of Coleman and Middlebrook [9] with modifications. Solutions of stearic acid were used as standards for this procedure.

Lipid phosphorus was determined by the method of Fiske and Subbarow [10] as modified in the chemistry laboratory of the Massachusetts General Hospital. An organic phosphorus control (glucose-6-phosphate) was run with each determination. Cholesterol was determined by the method of Zlatkis, Zak, and Boyle [11] with use of commercial cholesterol standards in acetic acid.

Microscopic controls were run with each set of analyses. The sudanophilic droplets were graded 0-to-4+ in epithelial and stromal cells separately. Per cent cell survival was estimated.

Results

The data obtained from experiments in which buttons were incubated in serum and sodium oleate are tabulated in the Table. These results express only the concentrations of the lipid fractions found in the buttons after incubation. They do not represent synthesis. To obtain figures for synthesis, it was necessary to compare the concentrations of lipid fractions found after incubation in oleate with concentrations of these same fractions in buttons which did not contain lipogenetic fat.

Summary of Data from Lipogenesis Experiments *

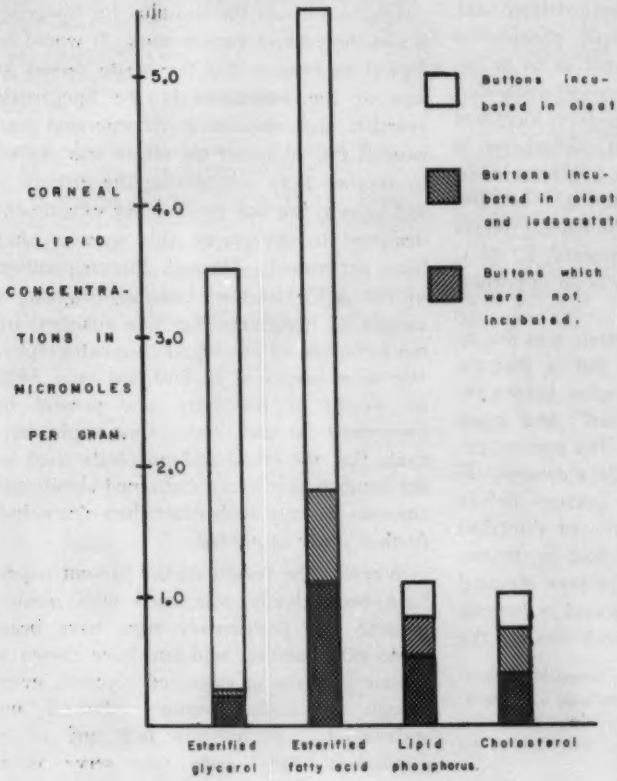
Exp. No.	Inc. Medium	Inc. Pd., Hr.		Esterified Glycerol	Esterified Fatty Acid	Lipid Phosphorus	Cholesterol
2	Oleate	48		2.52	4.90	1.09	—
2	Oleate	48		2.89	4.91	1.01	—
3	Oleate	48		3.42	7.09	1.05	1.07
3	Oleate	48		4.02	6.18	1.08	0.90
4	Oleate	48		4.72	4.40	1.15	1.12
			Av.	3.51±0.79 (S. D.)	5.50±0.99	1.08±0.05	1.03±0.16
3	Oleate & IAA	48		0	2.21	0.53	0.67
3	Oleate & IAA	48		0.52	1.22	0.41	0.63
4	Oleate & IAA	48		0.33	1.76	0.62	0.83
4	Oleate & IAA	48		0.28	1.99	0.60	0.83
			Av.	0.28±0.10	1.80±0.37	0.54±0.08	0.74±0.09
1	None	None		0.69	—	—	—
2	None	None		0	0.62	0.79	—
4	None	None		0	1.58	0.86	0.38
			Av.	0.23±0.33	1.10±0.48	0.83±0.04	0.38
Net synthesis: Ratio esterified fatty acid-esterified glycerol = 1.1				3.23	3.70	0.54	0.29

* All analytical values are expressed in micromoles per gram of wet weight per 48 hours' incubation. Esterified glycerol and esterified fatty acid values were calculated as described in the text. Each determination on a saponified sample is the average of two determinations. "Net synthesis" of a lipid fraction is the difference between average determinations of buttons incubated in oleate and buttons incubated in oleate and iodoacetate.

Kuwabara [12] and Hill et al.[13] have shown that sodium iodoacetate at a concentration of 5×10^{-3} molar in the incubation medium will inhibit completely aberrant lipogenesis in the rabbit cornea. Such incubations were run in the present experiments, the procedure being otherwise identical to that described for buttons incubated in oleate alone. In addition, a number of extractions were made from buttons which had not been incubated. The results of the iodoacetate experiments and of the unincubated buttons are shown in the Table.

It is seen that the concentration of esterified glycerol in buttons which had not been incubated averaged 0.23μM. per gram of cornea and in buttons which had been incubated in oleate and iodoacetate averaged 0.28μM. per gram of cornea. The concentrations of esterified fatty acid, lipid phosphorus, and cholesterol were likewise similar for these two series. It mattered little numerically which set of values were taken for comparison with buttons which had been incubated in oleate alone, but, for theoretical reasons which will be explained below, the buttons incubated in oleate and iodoacetate were chosen.

The concentration of esterified glycerol in the iodoacetate buttons, as has been mentioned above, averaged 0.28μM. per gram. The concentration of esterified glycerol in buttons incubated in oleate alone averaged 3.51μM. per gram. The difference between these two concentrations, 3.23μM. per gram, was taken as the "net synthesis" of esterified glycerol. The "net synthesis" of a lipid fraction therefore represents the amount of that lipid fraction manufactured by the



Data from the Table have been expressed in bar graph form. Bars representing values for buttons incubated in oleate, incubated in oleate and iodoacetate, and not incubated have been superimposed upon each other. "Net synthesis" of a lipid fraction by the buttons incubated in oleate is represented by how much the bar for buttons incubated in oleate exceeds the bar for buttons incubated in oleate and iodoacetate.

corneal buttons during the period of their incubation in serum-oleate medium.

The results listed in the Table are summarized graphically in the Figure. From these bar graphs it becomes apparent that in corneal tissues incubated with oleate there is a definite increase in the amounts of esterified oleate and glycerol. Since only slight increases are observed in the phosphatide or cholesterol fractions, it would appear that the material synthesized is a neutral fat.

Microscopically, the buttons incubated in oleate showed the expected 4+ lipogenesis; those incubated in oleate and iodoacetate showed negligible lipogenesis.

Comment

The lipogenetic fat synthesized by 1 gm. of corneal buttons incubated in sodium oleate and serum for 48 hours was found to be composed of 3.23μM. of esterified glycerol and 3.70μM. of esterified fatty acid. The "net syntheses" of lipid phosphorus and cholesterol were so small as to be insignificant, with use of the present methods.* The lipogenetic fat is therefore identified qualitatively as a neutral fat. Whether it is composed of mono-, di-, or triglycerides or a mixture of these is not known. The ratio of esterified fatty acid to esterified glycerol found in the present experiments, 1.1 to 1, suggests that monoglyceride is an important constituent.

Simms[14] felt that lipogenesis was due to a process of "phanerosis;" that is, that the lipogenetic fat had been present before incubation but was "unmasked" and made stainable during incubation. The present experiments do not support such a concept. If the neutral fat had been present before incubation, the concentrations of esterified glycerol and esterified fatty acid in the unincubated corneas would have been elevated to degrees similar to those found in buttons incubated in oleate alone. Such was not the case. A progress of active synthesis is necessary to explain the findings.

It was mentioned above that buttons incubated in oleate and iodoacetate were used for comparison with buttons incubated in oleate alone "for theoretical reasons." These reasons are that substances, especially neutral fat, not originally in the buttons before incubation might have been absorbed during the incubation. To demonstrate that such a simple, passive process did not account for the neutral fat "synthesized," the comparison was made with the iodoacetate corneas which had been incubated for a similar length of time. Any absorption should have occurred equally in buttons incubated in oleate alone and buttons incubated in oleate and iodoacetate. "Net syntheses," which are differences between the two values, would not be affected by any absorption and therefore must represent active synthesis.

Oleate ion was the stimulus for lipogenesis in the present experiments. It would be logical to assume that the oleate served as one of the substrates in the lipogenetic reaction and was being incorporated into neutral fat. Whether the oleate was altered to another fatty acid during the process is not known, but one preliminary experiment designed to investigate this question has been performed. Through the cooperation of Dr. A.T. James of London, England, a sample of lipogenetic fat was analyzed by the technique of gas-liquid chromatography. We were surprised to find that only 54% by weight of the fatty acid present in lipogenetic fat was oleate. One might conclude that the crude sodium oleate used in the incubation medium contained significant amounts of fatty acids other than oleate, but further study is needed.

Whereas the results of the present paper have been chiefly concerned with oleate-induced fat, preliminary runs have been made with palmitic acid and have shown a similar increase in esterified glycerol, even though histologic sections showed no sudanophilia. It appears that any of a number of fatty acids may serve as a

* Kuwabara and Cogan[4] have found histochemical evidence for phospholipid synthesis after incubation periods of 12 hours. Using incubation periods of 48 hours, however, they found no phospholipid.

substrate for fat formation and that the specificity of oleate lies only in the formation of sudanophilic fat.

Summary

The characteristics of the lipid substance produced during experimental aberrant lipogenesis in rabbit corneas were investigated by chemical analytic techniques. Determinations were made of the concentrations of esterified glycerol, esterified fatty acid, lipid phosphorus, and cholesterol present in corneas incubated in sodium oleate. These were compared with determinations made on corneas incubated in sodium oleate and sodium iodoacetate. Differences in concentrations were taken as "net syntheses."

Active synthesis of neutral fat in vitro was demonstrated.

Drs. David G. Cogan and Jin H. Kinoshita helped in the design of the experiments and the preparation of the paper.

243 Charles St. (14).

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Ocular Lesions in Xeroderma Pigmentosum

A Case Report of Carcinoma of the Cornea

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Xeroderma pigmentosum, also known as Kaposi's disease or lentigo maligna, was first described in 1870. It is a rare, progressive, precancerous disease of the skin and mucous membranes and frequently displays ocular complications. Mental deficiency has been noted in some patients. It tends to occur in the children of consanguineous marriages, being transmitted as a simple recessive character, and several siblings may have the disease. The pathogenic factor underlying the condition is considered to be a reaction of the surface epithelium to an abnormal organic or chemical disturbance within the body. Sunlight is the precipitating agent of this disease.

The patients usually have normal skins at birth. Xeroderma pigmentosum usually appears before the second year of life as a persistent erythema of the face, neck, and arms after exposure to sunlight but differing from ordinary sunburn in that it takes longer to disappear. This is followed by the gradual appearance of large "freckles" showing varying amounts of pigmentation on the exposed parts of the body. Eventually these pigmented maculae become darker in color and coalesce; the skin atrophies and takes on a parchment-like appearance, and blood vessels are seen between the "freckles," simulating telangiectasis. Neoplasms which show the structure of a granuloma, sarcoma, myxoma, angioma, or basal- or squamous-cell carcinoma may develop in the affected areas. The disease reaches its height between the sixth and seventh years of life. According to most authors, few patients afflicted with xeroderma pigmentosum survive to adulthood. The malignant changes have a predilection for the circumoral and circumorbital regions. Death may occur from intercurrent infection, from meningitis, or from hemorrhage following deep ulcerations which may destroy the orbital or nasal cavities.

Histologically the changes are those of irregular atrophy, dyskeratosis, telangiectasis, warty and malignant growths, with excessive deposits of melanin in the basal-cell and lowermost layers of the stratum spinosum as well as in the chromatophores in the upper dermis.

Eye complications in xeroderma pigmentosum are stated to occur in about 30%. Most of the cases with ocular manifestations described in the journals show primarily lesions of the lower lids, which may show erythema, pigmentation, atrophy, or malignant change. Atrophy of the lids leads to loss of the cilia, entropion, or ectropion, and not uncommon are symblepharon, ankyloblepharon, or loss of the entire lower lid. The conjunctivae, which are usually dry and hyperemic, may be the site of neoplasms, pingueculae, pseudopterygia, and phlyctenular-like lesions.

The corneal complications are rather characteristic. Atrophy of the lower lid may lead to exposure keratitis with secondary ulceration and opacification of the cornea with vascularization. The corneoscleral limbus is the site of predilection of benign and malignant tumors which may encroach on the cornea. Malignancy of the cornea in xeroderma pigmentosum is a very rare occurrence, only a few such cases having been reported in the literature. Epithe-

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From the Eye Service of Milwaukee Children's Hospital.

liomata extending for varying distances from the limbus onto the cornea are described by Saebø and Kamel, and Reese reported a case of xeroderma pigmentosum with squamous-cell epithelioma developing at the site of corneal ulceration. Iritis, iris atrophy, and abnormal iris pigmentation have been recorded. The crystalline lens and other structures of the eye are seldom involved.

Report of Case

The patient was born on June 19, 1951. His father and mother are third cousins.

Fig. 1.—Pigmentation, atrophy, and warty growths (some malignant) of exposed areas of head and neck.

There are five other children in the family, the two youngest having harelip and cleft palate but normal skin. At the age of one year, the patient was exposed to the sun and freckle-like pigmented areas began to appear on the face, scalp, neck, and upper chest, hands, and extensor surfaces of the arms. The pigmented maculae gradually became darker in color.

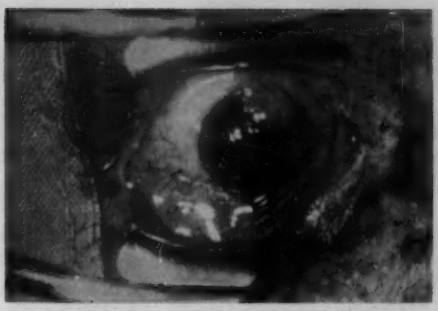
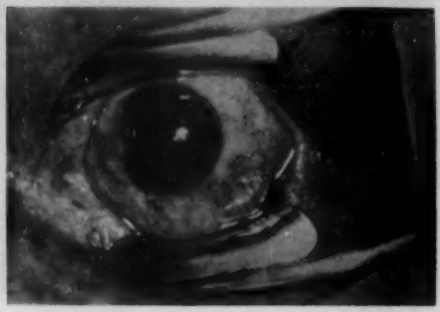


Fig. 2.—Mass of right cornea and limbus shown to be squamous-cell carcinoma on microscopic examination.

When he was first seen in a dermatology clinic, in January, 1956, at the age of 4½ years, the skin of the exposed parts of the body showed many pigmented patches varying in form, size, and degree of pigmentation. The skin was tense, dry, and scaly and the lips cracked. Scattered keratotic areas with ulceration and crusting were noted on the cheeks and nose. A psychological evaluation revealed an intellectually retarded, antagonistic, and apprehensive child.

As the facial lesions were very suspicious of malignancy, they were excised, and pathological examination proved them to be squamous- and basal-cell carcinomas. The patient returned after six months complaining of photophobia, conjunctival discharge, and agglutination of the eyelids. The underlying condition was felt to be a chronic blepharoconjunctivitis. Three new hyper-

Fig. 3.—Smooth, homogenous, nonvascular invasion of left cornea at limbus, showing epithelial hyperplasia on biopsy.



keratotic areas observed on the right cheek were subsequently electrodesiccated. The patient was examined again in June, 1957, when both lower lids were everted, resulting from atrophy and cicatrization of the skin of the face and lids. A pterygium-like lesion extending onto the cornea was also noted on the right eye. The palpebral conjunctivae were injected bilaterally, and there was some loss of cilia. A determination of the visual acuity was not possible owing to extremely poor cooperation, but there was evidence that the vision was good in each eye. Numerous new verrucae appearing on the face were electrocoagulated during the following year.

The patient was admitted on Aug. 20, 1958, for a lateral tarsorrhaphy of both eyes to correct marked ectropion of the lower lids, and at the time of surgery bilateral corneal lesions were noted. On the right cornea, an elevated pearly mass with vascular tufts was observed extending from the superior nasal limbus toward the center of the cornea. Inferior and continuous with this tissue, there was a pale, smooth, very slightly raised, nonpigmented lesion extending from the nasal conjunctiva onto the cornea. In the left eye, a flat, grayish, avascular lesion was encroaching on the cornea from the nasal corneoscleral limbus. The corneal lesion of the right eye and approximately 2-3 mm. of the adjoining conjunctiva were excised and the free edge of conjunctiva sutured to the sclera. Microscopic examination revealed the mass to be a squamous-cell carcinoma of low-grade malignancy. Two weeks subsequent to this procedure the tumor of the left cornea and limbus was excised under general anesthesia in the same manner. The pathologic report was epithelial hyperplasia of the cornea.

Postoperatively the patient did well, and examination under anesthesia two months later revealed a corneal opacification in the area of previous excision in the right eye. No evidence of tumor was grossly discernable. The left cornea was clear.

In summary, a case of xeroderma pigmentosum with carcinoma of the cornea is presented and the literature briefly reviewed. The lesion was treated by local surgical excision. More radical treatment was not undertaken, because the carcinoma was of low-grade malignancy and there are reports of cases locally excised without recurrence. Furthermore, useful vision remains in the eye and the prognosis is extremely poor for longevity.

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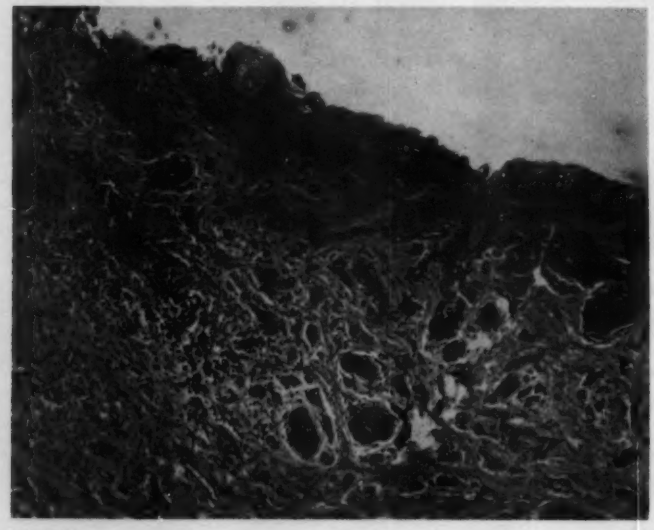

Fig. 4.—Squamous-cell carcinoma of cornea and limbus showing invasion of subepithelial tissues.

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Penetrating Keratoplasty in Rabbits

Effects of Beta-Propiolactone (BPL) Treatment of Donor Corneal Discs

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The problem of a storage technique for corneal tissue which will not impair its suitability for keratoplasty has been well reviewed recently,[1-4] and so any detailed consideration may be omitted. Suffice it to say that techniques involving freezing or freezing followed by dehydration of corneal material pretreated with glycerine represent substantial progress. However, a completely satisfactory solution of the problem remains to be achieved.

The chemical agent BPL (β-propiolactone) has been used successfully and apparently advantageously in the preparation for storage of arterial tissue to be used for arterial homografts.[5] A freshly prepared 1% solution of BPL is an effective virucide, bacteriocide, sporicide, and fungicide; however, after two hours at 38 C the initially toxic BPL has completely hydrolyzed into nontoxic degradation products. It has proved feasible to sterilize contaminated arterial homografts with BPL without destroying their usefulness as functional transplants.

We deemed it worth while to investigate the potential role of BPL-treated corneal tissue in optical keratoplasty, not because of its sterilizing effect but because of the possibility that it would destroy corneal stroma cells in such a fashion that their disintegration products might prove relatively nonantigenic and, if so, that the transplanted collagen framework might yield clear grafts.

Methods

Homologous centric penetrating keratoplasties were performed on three groups of rabbits: Group A: grafted with corneal discs pretreated with 1% BPL in 25% glycerin in isotonic saline; Group B: grafted with corneal discs pretreated with 25% glycerin in saline; Group C: grafted with fresh, untreated corneal discs from other rabbits (homologous controls). For two months after operation the animals were observed frequently relative to clarity of grafts. Tissue cultures were made of fresh corneal tissue and of corneal tissue pretreated as in Groups A and B to determine viability of graft material in terms of cellular proliferation and migration.

Young albino rabbits were used, of both sexes and weighing 2 to 4 kg. each; no attempt was made to determine genetic relationships. With a mechanical trephine 4 mm. penetrating grafts were taken from the central area of donor eyes. The grafts were placed centrally in recipient eyes and held in place by a continuous overlapping 000000 black nonabsorbable surgical (silk) suture, which was removed on about the 12th day.

Graft material for Group A was placed in freshly prepared, ice-cooled 1% BPL in 25% glycerin (by volume) in saline, immediately incubated at 38 C for two hours, then washed with saline, and used within half an hour. Graft material for Group B was treated similarly but without the BPL. Glycerin was used in these studies because it was found to minimize technically troublesome volume changes of the corneal tissue during the incubation period. For Group C the corneal material was grafted immediately after its removal. Tissue cultures were performed according to a standard technique,[4,6] using corneal material of full thickness.

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From the Department of Ophthalmology, Henry Ford Hospital.

This investigation was supported by a research grant from the National Institutes of Health.

Results

At the end of one month Group A included 19 opaque, 1 translucent, and no clear grafts; Group B included 14 opaque, 1 translucent, and no clear grafts, and Group C included 17 opaque, 5 translucent, and 13 clear grafts. The appearance of grafts one month after surgery was as follows:

	Group A (BPL in Glycerin)	Group B (Glycerin)	Group C (Controls)
Clear	0	0	13
Translucent	1	1	5
Opaque	19	14	17

At the end of two months Group A included 16 opaque and 1 translucent, Group B 13 opaque and 1 translucent, and Group C 13 opaque, 4 translucent, and 15 clear grafts. The appearance of grafts two months after surgery was as follows:

	Group A (BPL in Glycerin)	Group B (Glycerin)	Group C (Controls)
Clear	0	0	15
Translucent	1	1	4
Opaque	16	13	13

Once a graft in Group A or B became opaque (usually within one week), subsequent clearing did not occur. In Group C one or two showed clearing beyond that observed at one month. Only a small number of those grafts clear at one month tended to lose clarity. From the standpoint of ultimate healing alone, it was felt that grafts in Groups A and B approximated those in Group C.

In the tissue-culture studies, 40 exoplants of corneal tissue pretreated as in Group A and 80 exoplants of tissue pretreated as in Group B resulted in no growth, while 74 of 76 exoplants of fresh corneal tissue produced good growth of both epithelial and stromal cells. The results of tissue-culture studies were as follows:

	Group A (BPL in Glycerin)	Group B (Glycerin)	Group C (Controls)
Exoplants			
No growth	40	80	2
Showing growth	0	0	74

Comment

It is apparent that corneal tissue pretreated with BPL under the conditions noted above (Group A) resulted in grafts of poor optical quality, as did that of the glycerin-incubation controls (Group B). The tissue-culture studies indicated that in both groups nonviable grafts were being employed, and many reports now strongly suggest that viable tissue is required for successful optical keratoplasty. With respect to the use of 25% glycerin in the present studies, it is of interest that recent studies of corneal tissues exposed for only one hour at room temperature to various concentrations of glycerin have indicated that glycerin in excess of 25% results in less extensive migration in tissue culture and in gross physical changes in the tissue.[6]

From the standpoint of healing alone, the grafts of Groups A and B approximated Group C.

Conclusion

Exploration of BPL (β-propiolactone) in 25% glycerin saline mixtures from the standpoint of a possible role in storing corneal tissue for keratoplasty has yielded uniformly negative results.

Dr. Albert van Fossen and Dr. William Ferguson rendered valuable assistance in performing the corneal surgery.

Department of Ophthalmology, Henry Ford Hospital (2).

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Annual Reviews

Strabismus

Review of the Literature

WEBB P. CHAMBERLAIN Jr., M.D., Cleveland

During the year 1958 there has been increasing interest in the problems of amblyopia with emphasis on the management of patients with eccentric fixation. This concern with so-called pleoptics is exemplified by the position of importance accorded this subject in the opening of the Scientific Program at the Eighteenth International Congress of Ophthalmology in Brussels.

The worth-while contributions of these past months, however, have by no means been limited to this area, and they will be considered under the various subjects in the field of ocular motility.

The publication of "Strabismus Ophthalmic Symposium II," edited by Allen,[1] should be noted as a contribution to the books on ocular motility. There have been necessary alterations and additions to the original symposium of six years ago, and reference will be made to some of the papers by the indivual authors. Toselli,[2] at the University of Pisa, in Italy, has published a comprehensive book entitled "Heterophoria," which systematically presents the subject material on the diagnosis and treatment of the various types of phorias.

In this review, no attempt has been made to mention all of the publications which have appeared during the past year.

Nonsurgical Aspects of Strabismus

Amblyopia.—The term pleoptics was coined by Bangerter, of St. Gallen, Switzerland, and on the continent includes all treatment of amblyopia exanopsia by whatever method, including conventional occlusion.[3-5] In England and in the United States pleoptics has been used in the more limited sense to describe the diagnosis and treatment of amblyopia with eccentric fixation, with use of the visuscope, euthyscope, and coordinator as described by Cüppers. Beginning in Europe, on the continent, and then in England, and now in the United States, there has been mounting interest in various aspects of amblyopia.

In the opening symposium at the Brussels International Congress, Bangerter[6] introduced the subject of pleoptics. He emphasized the various types of amblyopia and their differing prognoses but stated that any case of amblyopia should now be considered curable. His plea was for early and intensive therapy. The basic training in the management of eccentric fixation is monocular, as has been reported in previous reviews. During this phase the eccentrically fixing eye is occluded, except when the monocular treatment is being carried out. Once central fixation has been established in the amblyopic eye, occlusion is then shifted to the good eye. In due course conventional binocular orthoptic treatment may be undertaken. Bangerter emphasized the importance of proper "after-training" to consolidate the normalized motor and sensory correlation. In continuing the discussion, Lyle stressed the "after-image" treatment of Cüppers and further pointed up the value of a proper orthoptic follow-through in establishing efficient postsurgical binocular function.

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On the continent of Europe, the treatment of eccentric fixation by the methods of Bangerter and Cüppers has been long established. Fessl[7] reports on 15 years' experience at the Bangerter pleoptic school. He stresses the vital role of a precise diagnosis of eccentric fixation, and contends that occlusion of the good eye in a patient with eccentric fixation is definitely harmful.

In France, Hugonnier[8] reports favorable results with Cüppers' methods and Pigassau and Chadbourne[9] emphasize the importance of intensive treatment, carried out even twice daily where possible. Sedan[10] has written a monograph on the problem of maintaining the vision attained in the amblyopic eye. Charles Thomas[11,12] has published two papers relating to his specific instrument, the "foveo-fixator," and his "star test" for use in the treatment of amblyopia. In Holland, Jonkers[13] states that the successful treatment of comitant strabismus depends on a well-considered combination of surgical, pleoptic, and orthoptic procedures.

Ehrich[14] reports from Germany a series of 74 cases with eccentric fixation who were evaluated before and after surgery but received no orthoptic or pleoptic treatment. He found that in 34 of these patients the fixation of the amblyopic eye was altered after surgery and in 29 of these the change was to a more favorable position.

Blatt and Regenbogen,[15] in Romania, report an incidence of only 2.7% eccentric fixation in a series of 220 children with comitant strabismus. Further to the east, in Russia, Belostotsky and Friedman[16] report favorable results with Cüppers method of treating amblyopia with eccentric fixation.

Kamal Salman[17] reports at the First Afro-Asian Congress of Ophthalmology that an orthoptic clinic has been established in Lebanon with facilities for carrying through Cüppers' pleoptic treatment of eccentric fixators.

Von Noorden and Burian[18] have recently studied the dark-adapted amblyopic eye and demonstrated with electro-ophthalmography that there is normal fixation ability in the dark. On this basis they have developed a method of treating strabismus amblyopia. Oppel and Kranke[19] have also studied dark-adaptation in amblyopia and found a characteristic pattern. Gernet,[20] in Geneva, reports on the use of polarized lenses set at variable angles in a spectacle frame so as to afford partial occlusion of the dominant eye. Using these polarized filters the light intensity can be reduced 80% to 100%, creating a dark-adapted eye with the physiological central scotoma that is present in night vision.

In England, there continues to be considerable interest in the various aspects of amblyopia. Perkins[21] believes that "amblyopia of arrest" is rare and that most amblyopia is secondary to active suppression. Pugh[22] and Mayweg and Massie[23] have indicated the importance of the specific manner in which amblyopia visual acuities are tested. They point to the discrepancy between acuities tested with the isolated letter and those in which the patient views the whole line. As is well known, "angular visual acuity" with the isolated letter is considerably better than "cortical visual acuity" where several characters may be seen at once. It is obvious that results cannot be compared unless precisely the same method of testing is used on every occasion. Downey[24] indicates that the incidence of eccentric fixation in England seems to be much lower than that reported on the continent. Douthwaite and Lee[5] stress the proper selection of cases as vital to success in pleoptics. Without wholehearted cooperation by the patient this complex routine is doomed to failure. Foster[3] and Wybar[4] describe their experience with the visuscope, euthyscope, and coordinator. Schlossman,[25] in New York, reviews a series of 180 amblyopes and compares the results of treatment by occlusion alone and by the after-image method of Cüppers.

Occlusion in the treatment of suppression amblyopia was the subject of the panel at the Chicago Orthoptic Symposium in 1957.

This included half-lens occlusion of the temporal or nasal halves and total occlusion. Swenson [26] discusses temporal occlusion of the lens before the convergent eye in the treatment of amblyopia with eccentric fixation. She reports improved visual acuity and reduced angle of squint, as well as change in the character of fixation of the amblyopic eye. Stelzer [27] presents occlusion of the nasal half of the lens before the diverging eye for the correction of suppression in exotropia. Swift [28] discusses the role of total and constant occlusion of the dominant eye in treating amblyopes with central fixation. She also mentions the usefulness of occlusion in improving motility, particularly abduction of the convergent eye. Swift, Purcell,[29] and Stelzer [30] comment on the seemingly paradoxical phenomenon of visual improvement following total occlusion of the deviating eye in amblyopia with eccentric fixation.

Continuing their study of the effects of hypnotic suggestion on suppression amblyopia, Browning, Quinn, and Crasilneck [31] report significant gains in visual acuity, particularly at close range.

Accommodative Strabismus and the Use of Miotics.—Costenbader [32] ties together the several aspects of the nonsurgical management of strabismus including refraction, correction of amblyopia, treatment of defective binocular vision, and the use of drugs. He recommends DFP (Floropryl) in 0.01% to 0.03% strength daily in accommodative convergence excess and states that hyperopes of less than 4 D. may eventually learn to see well and comfortably while keeping the eyes straight without glasses. Stephenson,[33] in England, uses DFP 0.1% daily for the first two weeks and then changes to alternate days. Edwards [34] urges the substitution of pilocarpine where prolonged therapy is indicated, in order to avoid the development of iris cysts. Abraham [35] recommends pilocarpine and DFP but still believes that iris cysts are no contraindication to DFP when used with proper supervision.

Parks,[36] investigating abnormal accommodative convergence in esotropic and exotropic children, found that more than one-half of each group showed over 10 D. difference between distance and near fixation. This he attributes to an abnormal accommodation and accommodation convergence innervation (A:AC), which causes an exaggeration of "eso" at near but a reduction of "exo" as close range. In accommodation convergence excess DFP normalizes the A:AC while it is used, and in older children it seems to have a lasting benefit even after discontinuation of the drug. Parks reports that a spontaneous improvement in the abnormal A:AC can be expected in one-half of children with strabismus.

Orthoptics.—In a timely editorial by Cooper,[37] Executive Secretary of the American Orthoptic Council, the present status of orthoptic practice is outlined. The orthoptist is properly defined as a medical auxiliary, legally and professionally dependent on the ophthalmologist whose patients she treats. The American Orthoptic Council, with its representatives from the four major ophthalmological organizations, serves in a sponsoring and supervisory capacity relating to the education, certification, and professional activity of orthoptic technicians.

As to the general value of orthoptics, Fleming [38] found two-thirds of her series of 50 consecutive referrals were apparently benefited by orthoptic treatment. Walraven [39] suggests the usefulness of properly prescribed home exercises even in a patient of unfavorable prognosis who could not make regular or frequent visits to the orthoptic clinic. Berens, Brackett, and Taylor [40] recommend diverging exercises with the prism bar, while maintaining fusion on small print, as beneficial in patients exhibiting overconvergence in reading. Parsons and Salisbury [41] would treat accommodative convergence excess with orthoptics rather than miotics, attempting thereby to improve coordination of the accommodation convergence relationship. Sutcliffe [42] urges the use of dissociation exercises in the management of accommodative convergence excess.

Mary Kramer [43] emphasizes the importance of controlling suppression during the binocular training of accommodative esotropes. In addition to proper refractive support, partial occlusion should be used as indicated.

In Italy, Caprara [44] points to the association of convergence insufficiency with esophoria or low-grade hyperphoria as well as exophoria. Symptoms are related to the use of the eyes in close work and particularly to the temperament of the patient. Orthoptic exercises are highly beneficial. Nawratski and Avrouskine [45] further emphasize psychogenic factors in convergence insufficiency and observe that symptoms are often far out of proportion to the objective findings. They suggest psychotherapy for the anxiety and fear of failure. Ten Doesschate,[46] in Amsterdam, however, cautions against ascribing symptoms to mild degrees of heterophoria when they may really be due to basic psychological factors. The relief of symptoms by orthoptic exercises in patients with psychogenic factors is obviously difficult to evaluate.

Berke [47] studied the value of orthoptic exercises in achieving postoperative third-degree fusion and found that amblyopia of 20/50 or worse in one eye prevented a functional result. He found in his series of 256 patients that orthoptics were useless in the presence of a residual horizontal deviation of over 10 D. or a hypertropia of more than 2 D. Orthoptic exercises were of little apparent help in improving the good results expected when a deviation has been present less than 50% of the patient's lifetime. Orthoptic exercises were unnecessary in attaining a functional result in intermittent squint, because 100% of such patients developed third-degree fusion without exercises. In constant squint dating from birth, postoperative third-degree fusion was not obtained even with extensive orthoptic exercises. He concluded that in only 5% of cases were orthoptic exercises apparently indispensable in attaining a functional result. Berke [48] emphasizes that no statistics of postoperative functional results are valid unless the nature of the case and the age of onset are considered, as well as the criteria for a functional result.

In discussion, Costenbader [49] did not agree that congenital strabismus never obtains a functional result or that orthoptics is of no value. He suggests that patients with poor vision be given active and energetic treatment for amblyopia and suppression.

Kraft and Hötte,[50] in Germany, favor surgery as the first step in the treatment of amblyopia, stating that vision improves in many amblyopic eyes even with eccentric fixation after the alignment has been corrected. Where pleoptic treatment is still necessary, they observe that the euthyscope can be used more efficiently when the eyes are straight. Such patients have been hospitalized as long as seven weeks after surgery, while pleoptics is carried out. Again, there are obvious economic difficulties involved in considering such an intensive and prolonged routine in this country.

With reference to this problem of fusion after surgery, Parry [51] investigated long-term end-results in a selected series of 49 concomitant strabismus cases 10 years after operation. Twenty-one patients had fusion before surgery and at the time of discharge, and all had retained this fusion. Five patients discharged cosmetically straight but without fusion had acquired single binocular vision and some fusion. Twenty patients discharged cosmetically straight had remained in good alignment. These surprisingly good results perhaps indicate that unhappy patients do not return for a long-term check-up.

In lecturing on normal and anomalous retinal correspondence, Burian [52] provides a critical review of recent publications on this subject, bringing up to date some of the concepts and terminology on the sensory relationships of the retinas in comitant strabismus. He indicates that there are still the two schools, (1) those who believe ARC is a serious obstacle to the attainment of binocular vision that should and can

be adequately treated before surgery and (2) those who believe that there is no relation between surgical results and the status of retinal correspondence. He points to the need for a proper study and evaluation of this problem by qualified experts in this field.

Görtz [53] describes the phenomenon observed in the treatment of anomalous retinal correspondence in which the angle of anomaly may gradually decrease until the subjective angle and the objective angle are the same and there is normal retinal correspondence.

Acute Concomitant Esotropia: Reports on concomitant esotropia of acute onset in more mature patients have led to some confusion in the literature as to the nature of this condition and its proper diagnosis. Burian and Miller [54] describe three types: (1) those following artificial interruption of fusion, such as seen after patching for foreign body; (2) strabismus of the Franceschetti type, characterized by acute onset with diplopia, large angle of squint, absence of any paralysis, and good potential binocular cooperation; (3) acute esotropia of the Bielschowsky type, characteristically with myopic refractive error, onset with psychic or physical shock, crossed diplopia for distance but no true paralyses, although perhaps slight limitation of abduction. They conclude that acute comitant esotropia does not differ basically from other esotropias, although the course and symptoms are influenced by the more mature age at the time of onset. Amidei,[55] Pascal,[56] and Meisner [57] add case reports of acute concomitant strabismus.

Diagnostic Instruments and Methods.— Stanworth [58] has modified a major amblyoscope so that conditions more nearly simulate everyday use of the eyes. It makes possible an evaluation of the angle of squint and the patient's binocular status but supposedly reduces so-called instrument convergence.

Krüger [59] describes an electronic flash in the shape of a star and states that it is helpful in teaching children to recognize an after-image.

Viefhues and Kuhnhardt [60] criticize vision-testing in amblyopia that depends on the observation of moving alternate black and white lines and the objective determination of that thickness of line where optokinetic nystagmus stops. They believe visual acuity obtained in this manner is inaccurately high because light sensitivity of the retinal periphery and not true visual acuity is recorded. Grzibek and Sachsenweger [61] use a similar method of objective visual acuity measurement with use of a rotating drum and observation of the point of termination of optokinetic nystagmus. Recognizing the limits of this method, they feel that it still has value.

Walter [62] recommends modified clocks in checking visual acuity, with black blocks replacing the numbers on the dial, and believes it is a useful screening method. For testing vision in children, Jonkers [63] concludes that letters or symbol E's are superior to pictures, numbers, or the Landolt rings. Fonda [64] urges the use of the standard vision charts at shorter ranges to give better gradation in the evaluation of amblyopes of high degree. The child should be tested at 10 ft. or less when vision is below 20/200. Deering [65] places emphasis on preschool screening for eye defects, because a valuable opportunity to treat amblyopia has already been lost by the time school age is reached.

Pavia Lijo [66] suggests the use of a double exposure of the squinting eye as a means of photographically evaluating eye position on the basis of the corneal reflex from a single light source. One exposure of the squinting eye is taken with the dominant eye fixing, and a second exposure of this eye is taken with the deviating eye fixing. The two light reflexes are thus recorded on the same film, and any shift in position may be noted.

Trotter and Stromberg [67] describe a linear electronic flash tube for use as the light source in the after-image test for determining retinal correspondence. In spite of its very short duration, the high intensity of

light affords a vivid and persistent afterimage. Because only momentary fixation is required, younger children may be tested by this device.

A short method of treating anomalous retinal correspondence is described by Tibbs [68] that includes total occlusion, work on the major amblyoscope, and carefully prescribed home exercises on her tracograph.

For use in offices or clinics handling a volume of motility patients, a punch-card clinic record is recommended by Wheeler.[69] This permits easy evaluation and analysis of clinical or surgical material on strabismus patients.

Keeney and Duerson [70] have devised a near-vision card based on the Snellen principle, incorporating simplified sentence structure, letters of the same size, and a minimum glare.

General Aspects of Surgical Treatment

In the management of strabismus surgery there continues to be emphasis on early surgery and symmetrical surgery. Perhaps there has been less reference to the so-called "AV syndrome."

Relating to the general complications of surgery is the problem of the oculocardiac reflex which was investigated with electrocardiograms during eye-muscle surgery by Bosomworth, Ziegler, and Jacoby,[71] working at Ohio State. They found slowing of the pulse in 23 out of 28 patients. Additional disturbances including nodal rhythm, auriculoventricular block, and bigeminal rhythm were experienced in nine patients, and the greatest alterations followed traction on the medial recti. In no case was the oxygen or carbon dioxide content of arterial blood abnormal. Intravenous atropine seemed to reduce the incidence of cardiac changes, especially in the first half-hour. Surprisingly enough, the use of retrobulbar injection was not effective in eliminating changes in the cardiac rate or rhythm. The authors conclude that a careful monitoring of the pulse during surgery on the eye muscles is essential.

In contrast, Rhode et al.,[72] in Caracas, Venezuela, studied clinical cases and experiments on dogs and concluded that muscle surgery could not be responsible for cardiac arrest but that these accidents observed by others were due to anesthesia.

In New Zealand, Ring [73] has adopted the symmetrical surgery approach to the treatment of concomitant esotropia in young children. He recommends a recession of each medial rectus to a maximum of 5 mm. and combines this with a bilateral myomectomy of the inferior oblique when there is significant overelevation on adduction. He prefers to operate by 3 years of age and considers himself unconventional in not patching either eye.

Tour and Asbury [74] also report a preference for symmetrical surgery in esotropia and have found good results with 4 mm. bimedial recessions but overcorrections with 5 mm. bimedial recessions.

Lavat and Canque,[75] in France, favor symmetrical surgery combined with proper orthoptics. In Britain, Bridgeman [76] makes a plea for early surgery in congenital squints, frequently operating by 9 to 12 months of age.

Haensel [77] agrees with myomectomy of the inferior obliques at their origins in patients with elevation of the adducted eye. This is urged as early as one year of age and apparently in combination with appropriate symmetrical surgery of the horizontal rotators.

Reports have appeared from various countries relating to oblique surgery for treatment of the so-called "A-V syndrome." Urist [78] contends, however, that the "A" and "V" syndromes can be caused by dysfunction of the primary horizontal rotators. In the "V" syndrome, with apparent overaction of the inferior obliques, the dysfunction is due to overaction of the medial recti in "V eso" and overaction of the lateral recti in "V exo." In the "A syndrome," with apparent underaction of the inferior obliques, the primary dysfunction is under-

action of the lateral recti in "A eso" and underaction of the medial recti in "A exo."

There are a number of publications relating to specific surgical techniques. In Toronto, Morgan and Arstikaites [79] report on their recent success with marginal myotomies as a substitute for the recession operation on the medial rectus. They have experienced 91% good results with only two cases losing convergence. They hope that long-term follow-ups will show fewer cases of secondary divergence.

In Holland, Huijsmans [80] reports on the results of a stretching technique applied to the eye muscles after use of a hyaluronidase preparation. He apparently was able to eliminate some of the overaction of muscles by this method of stretching with fixation forceps. He has experienced no case of cardiac arrest but does his procedure under anesthesia with retrobulbar akinesia.

From Jugoslavia, Sokolic [81] describes a modified tucking procedure which apparently involves a double folding of the muscle, which he believes is more secure than the conventional tuck. Lavat,[82] in Paris, reports on his use of the O'Connor method of muscle shortening. He removes the suture once he is satisfied with the degree of correction and particularly recommends this procedure for the vertical muscles.

Despite the emphasis that has been placed on symmetrical surgery, Urist [83] points out that there are still situations that specifically call for asymmetrical surgery. In a paretic or incomitant defect it is obvious that an asymmetrical procedure may be necessary. As would be expected, the greatest effect is in the field of action of the muscle in question, e. g., the medial rectus on adduction, the lateral rectus on abduction. In combined surgery, the greatest effect is in the direction of the recessed muscle, e. g., the direction of the recessed medial rather than the resected lateral in esotropia and the direction of the recessed lateral rather than the resected medial in exotropia.

Exotropia.—In discussing exotropia, Jampolsky [84] points out that this is characteristically a disorder of "visual adults." Constant exotropia is characterized by profound sensory motor anomalies, in contrast with exophoria and intermittent exotropia. For the surgical treatment of monocular exotropia he recommends a full recession of the lateral rectus up to 8 mm. combined with a resection of the medial rectus. In constant alternating exotropia of large degree he would operate on all four horizontal recti at one session, doing a full bilateral recession of the lateral recti, a full resection of one medial, and a lesser shortening operation on the other medial.

In considering divergence excess, Johnson [85] follows Costenbader's criteria: (1) exophoria or exotropia for distance but normal binocular alignment for near; (2) intermittence; (3) near point of convergence and prism convergence good. The author favors a bilateral recession of the lateral recti of 7 to 9 mm. regardless of the amount of deviation. He has found that smaller amounts of surgery in deviations of less than 25△ exotropia give disappointing results, and the resection-recession operation was found to give incomitance and less percentage of binocularity. The presence of an associated vertical imbalance had surprisingly little effect in preventing good correction when the proper horizontal surgery was done. Patients with myopia apparently had a poor prognosis. Cases with less than 25 D. exophoria-exotropia had the best postoperative results.

In his lectures on divergent deviations, Knapp [86] deals with various aspects of this problem. He quotes that 85% of divergence anomalies are intermittent, becoming manifest only at different times and at different distances. Present terminology seems to favor the term intermittent exotropia in describing these cases. Knapp comments that a large percentage of so-called divergence excess patients may be exophoria at 20 ft. but exotropia at 200 ft. or when attention wanders. He finds prism measurements inadequate by themselves in evaluating the importance of the degree of

intermittency. A surprisingly small percentage of these intermittent exotropias will go on to constant exotropias for distance and near.

With reference to the treatment of intermittent exotropia, Knapp agrees that correction of refractive error is of negligible benefit, as is overcorrection with minus spheres. Orthoptic converging exercises are of questionable help and may lead to overconvergence if the child later requires surgery. However, antisuppression exercises aimed at eliminating the hemiretinal suppression may certainly be of great benefit. Every patient should, if possible, be taught consciousness of diplopia when the eyes are deviating, if necessary with use of a colored filter. Knapp would seem skeptical that intermittent exotropia can be cured by the routine outlined by McPhail but feels orthoptics should be used only as a supplement to surgery in these patients with divergence excess.

Vertical and Horizontal Noncomitant Strabismus.—A prominent contribution to the subject of incomitant vertical strabismus during recent years has been Brown's recognition of the so-called "sheath syndrome of the superior oblique" as a factor in apparent paralysis of the inferior oblique. His thesis,[87] published in 1958, on "Isolated Inferior Oblique Paralysis" details the diagnosis and management of this condition. In evaluating 97 cases he concludes that structural anomalies of the inferior oblique itself can be ruled out as a cause of complete paralysis of this muscle. In addition to a shortened anterior sheath of the superior oblique, he believes there may be in some cases a defect at the neuromuscular junction of the involved inferior oblique.

In diagnosis of sheath syndrome Brown enumerates (1) complete paralysis of the inferior oblique with inability to elevate the eye in full adduction; (2) little if any secondary contracture of the opposing superior oblique; (3) the ability to elevate the eye increases in a straight line progression as the eye is abducted; (4) muscle balance in the temporal field is normal; (5) the palpebral fissure of the affected eye widens as the eye is adducted; (6) the horizontal position of the eyes in the straight-ahead position may become divergent as the eyes are moved upward.

Surgery is not indicated in a patient with sheath syndrome who has fusion in primary position and in the reading position without tilting the head.

Costenbader and Albert[88] report spontaneous regression in a patient with pseudoparalysis of the inferior oblique, indicating that anatomical anomalies do not account for all cases of inferior oblique underaction.

Agenesis of the medial rectus muscle has been treated successfully with split tendon transplants from the vertical recti by Girard and Neely,[89] duplicating again Hummelsheim's original monkey experiment. They point to the danger of iris necrosis and iridocyclitis after simultaneous detachment of all four rectus muscles.

In Italy, Toselli and Guzzinati[90] and in Britain, Johnstone[91] report on the effectiveness of the classical Hummelsheim procedure for correction of sixth nerve paralysis by transplantation of the split tendons of the vertical recti to the lateral rectus.

Tenon's capsule has been used by Adler[92] to repair muscles which have been destroyed surgically. Tongues of the fascia are brought forward and attached to the muscle stump. He found a surprising improvement in the appearance and function, suggesting some connection with the retracted muscle.

The differential diagnosis between bilateral sixth nerve paralysis and divergence paralysis is discussed by Bedrossian.[93] He states that in divergent paralysis the fields of fixation extend temporally in the lower field, whereas in bilateral sixth nerve paralysis fixation is limited in the entire temporal field.

In a review of 1,000 cases of paralysis of the third, fourth, and sixth nerve, Rucker[94] reports no cause was found in 28% and head injuries accounted for 17%, brain tumor 17%, vascular disease 15%, and aneurysm of the circle of Willis 11%.

Diabetic neuropathy was designated as the cause of extraocular muscle paralysis in six cases reported by Snydacker.[95] With proper control of diabetes the prognosis is supposedly good.

In the diagnosis of isolated cyclovertical muscle palsies, Parks[96] emphasizes the ease with which one may determine whether the hypertropia increases on dextroversion or on levoversion. Then it is also a simple matter to ascertain whether the hypertropia increases when the head is tilted to the right shoulder or to the left shoulder. As a general principle in surgery of the vertical rotators, he would operate to weaken the direct antagonist if there is contracture. Otherwise the procedure of choice would be a recession of the normal yoke muscle, providing there is fixation with the paretic eye.

Hugonnier[97] observes that ocular torticollis can pass unnoticed unless the possibility is kept in mind. While a head tilt is not an infallible sign of a vertical muscle anomaly, it is often a clue and aid in diagnosis. A compensatory head tilt is considered an indication that fusion is present.

Girard[98] describes his method of inferior oblique recession performed after detaching the lateral rectus and with freeing of fascial connections. He quotes Berens' rule that 1 mm. retroplacement of the inferior oblique will provide 1△ correction in primary position or 2△ in the field of action of the inferior oblique.

Basic Science

A number of papers dealing with basic science have already been considered in relation to the various aspects of ocular motility.

Breinin[99] completed his series on electromyography in ocular and neurologic diagnosis with a section on supranuclear lesions. In a brain-tumor patient with an esotropia greater on distance fixation—a divergence paralysis—there was decreased innervation to the lateral recti, which would be in accord with the concept of a divergence center. He concludes that the extraocular muscles "behave in a manner consonant with classical Sherringtonian physiology."

Breinin[100] also published a comparison of the electromyography of ocular and peripheral skeletal muscles, revealing a fundamental similarity. Integrating techniques and the various circuits are described. The combination of electronic integrating and differentiating techniques open new avenues of investigation.

Electromyographic studies on asymmetric convergence were carried out by Tamler, Jampolsky, and Marg.[101] They report a simultaneous increase in electrical activity of both medial and lateral rectus muscles of the stationary eye. This finding is in agreement with Hering's theory that there is a balance between vergence and version stimuli in the stationary eye.

A significant electromyographic contribution by Miller[102] points out that very quick versions or saccadic eye movements are induced by a sudden burst of motor activity which is followed by an orderly firing pattern. In contrast, electromyograms of vergence movements have a slow acceleration which persists over a longer period.

In Japan, Momosse[103] evaluated quantitative measurements of action potentials of eye muscles with use of the integrator. In horizontal movements he found the vertical rotators maintaining a constant level of electrical activity, supporting the concept of cocontraction.

Nawratzski and Jampolsky[104] demonstrated a marked nasal temporal hemiretinal difference in amblyopic exotropes, with use of a special adaptation of the Harrington-Flocks screener.

The different theories of stereopsis have been summarized and evaluated by Ogle.[105] He indicates the usefulness of Hering's concept of retinal depth values. He observes that stereopsis is somehow related to the processes of fusion in binocular vision. Ogle points out that it is possible to judge the distance of objects even if their images are so disparate as to produce diplopia. Depending on whether the double images

are crossed or uncrossed, they appear farther or nearer than the fixation point. Ogle and Weil [106] report that there is a rapid decrease in stereoscopic acuity associated with reduction in the time exposed to the stimulus. Regardless of how short the exposure time, however, the stereoscopic impression occurs immediately. There is no delay between the instant of exposure and the depth response, such as might be expected if a cortical elaboration of the stimulus was required.

Sachsenweger [107] indicates the various aspects of sensory fusion in the normal person. He demonstrates that in binocular vision an object seems to be displaced to the side of the dominant eye.

In the last Annual Review on strabismus, Parks [108] summarized the status of fixation disparity. This year, Ogle [109] has contributed to this interesting academic discussion a paper relating fixation disparity and ocular muscle imbalance. It is his opinion that fixation disparity may prove to be a useful tool in the investigation of more mature patients.

Studying the etiology of concomitant strabismus, Doden [110] examined strabismic patients with Jung's electronystagmographic method and found nearly 50% of this series had lesions of the opticovestibular coordinations which take place in the brain stem.

Cogan [111] describes some interesting objective and subjective observations on the vestibulo-oculo system resulting from loss of labyrinthine function. These indicate the important role of the normal labyrinth in fine fixation and follow movements.

A temporary artificial paresis of extraocular muscles has been produced by Schenk [112] with the injection of "Rhaetocaine," the akinesia persisting as long as one week. He suggests a possible use in surgically overcorrected strabismus.

Knoll [113] has devised torsion demonstrations with a Gimbal projector which can be rotated around the axes of Fick, thus stimulating the situation in rotations of the globe. It is suitable for teaching and shows the amount and direction of torsion or wheel rotation as the eye is carried into the tertiary positions.

Rados and Scholz [114] describe a case of pseudostrabismus due to heterotopia of the macula. Although there seemed to be a gross deviation of the eye, there was no shift on covering. This constitutes a large anomaly of the angle-κ on a pathological basis. A somewhat similar case has been reported by Hugonnier and Royer,[115] who describe a patient with pseudostrabismus simulating exotropia due to displacement of the macula by retrolental fibroplasia.

Jacobson et al.[116] have studied the electrical activity of the ciliary body with use of a microelectrode fastened in a contact lens. There seem to be electrical discharges associated with accommodation.

The relationship between vergence and accommodation has been studied by Alpern,[117] who demonstrated that changes in target size can produce changes in vergence even when accommodation is held fixed. He has also shown that accommodative vergence follows accommodative response even when the accommodative stimulus remains fixed.

There are a number of good publications that have been omitted from comment in this review on strabismus. Some of these are listed in the added bibliography, where they may be available as reference material.

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Correspondence

MULTIPLE TARGETS IN VISUAL FIELD EXAMINATIONS WITH A TANGENT SCREEN

To the Editor:—In the November, 1958, issue of the A. M. A. ARCHIVES OF OPHTHALMOLOGY, Dr. Robert W. Zeller has written a paper called "Multiple Targets in Visual Field Examinations with a Tangent Screen," wherein at the end of the summary he kindly credits me with the following: "The use of paddles to carry targets in tangent screen work was first suggested to me by Dr. Max Chamlin several years ago. To my knowledge, however, he has not used more than one target on the paddle."

Since Dr. Zeller makes a special point of the use of multiple targets on one paddle, I would like to correct his impression by referring him to a paper entitled "Minimal Defects in Visual Field Studies," which I read before the Section of Ophthalmology, New York Academy of Medicine, April, 1948, and had published in the *Archives of Ophthalmology* in August, 1949 (42:126-139). In this article, on page 138, I describe the paddles mentioned, with two test objects instead of one, mounted on the same carrier.

Dr. Zeller then goes on to describe the technique of picking up level differences and qualitative differences on both sides of the vertical meridian. The basic concepts of these techniques are fully described in my 1948 paper mentioned above on pages 129 and 134.

He then applies the principle of simultaneous stimulation to pick up very early central defects. Actually, he compares central area with eccentric area at the same time. This is not a very safe technique for picking up minimal defects because he is comparing two areas which are unequal in visual efficiency to start with and therefore may easily miss an early central defect. Actually, this principle could be made applicable for detection of early caecocentral defects if one places a test object in the caecocentral area between 3 and 10 degrees from fixation and another one on the other side of fixation equidistant from the fixation point. Thus, one compares two areas of field which are normally equal in visual function and can thereby pick up really minimal differences.

A much more important and clinically useful application of the same principle is the detection of early nerve fiber bundle defects with use of test targets simultaneously above and below the horizontal line on the nasal side of fixation, as in early cases of glaucoma. These methods of use of multiple targets on the conventional tangent screen will be found in the brochures put out annually by the American Academy of Ophthalmology and Otolaryngology describing my course in perimetry on "Techniques for the Detection of Minimal Defects." These have been in print annually for at least five years.

Finally, a word about the choice of test objects that Dr. Zeller suggests. He says, "the size of a test object used will vary with the visual acuity of the patient being tested."

Since the central visual acuity depends on the quality of the field almost immediately around fixation, that is, for a distance of 2 or 3 degrees, it would be wrong to lay down a rule of thumb for the size of test objects when testing the area about 10 degrees or so from fixation, which is the area most frequently tested for early minimal defects as in chiasmal tumors. For example, if there should be a central scotoma involving 2 or 3 degrees of field around fixation, visual acuity may be reduced to a very marked degree, but, nevertheless, the field at 10 or 15 degrees may be perfectly intact and therefore a 1/2,000 test object may still be utilized very readily in that area. This point is much more thoroughly discussed in my article entitled "Choice of Test Objects in Visual Field Studies" (*Am. J. Ophth.* 35:381 [March] 1952).

A basic principle involved in the use of simultaneous stimulation for minimal defects is to use minimal stimuli for the particular isopter being examined. On the tangent screen, such a minimal isopter is that for 1/2,000 white, and this has been well known since 1915, when Dr. Walker first described the value of this test. The use of a 3/2,000 white, as Dr. Zeller suggests, is not a minimal test in this area. Furthermore, reliance on 3/2,000 white in this area may easily lead to an oversight of a defect which can readily be picked up with 1/2,000 white, even without simultaneous stimulation. As a matter of fact, it would seem to me that if such defect is to be picked up with simultaneous stimulation with use of 3/2,000 white, there might easily be an absolute defect for 1/2,000 white.

To pursue this point further, the isopter for 3/2,000 white undoubtedly reaches out to about 28 to 40 degrees.* Therefore, minimal testing with 3/2,000 white would be applicable in the area somewhere beyond 20 or 25 degrees, up to 28 and 40 degrees, an area beyond clinical usefulness on the usual tangent screen. For the above reasons, as described in the brochures on minimal techniques describing my course at the Chicago meetings in October. I have been advocating the insertion of two 1 mm. white pins into comparable areas of the tangent screen for simultaneous stimulation, preferably between 8 and 15 degrees from fixation and well to either side of the vertical meridian, particularly for detecting early evidence of chiasmal interference.

The development of new techniques for the application of established principles is to be encouraged. However, even new techniques should be guided by the limits of those basic principles involved.

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*In an article recently published in the A. M. A. ARCHIVES OF OPHTHALMOLOGY (61:608 [April] 1959) entitled "An Isopter in the Intermediate Field of Vision," I have found the isopter for 1.3/750 white to extend to between 32 and 48 degrees. The visual angle for 1.3/750 is 0.099 degrees. The visual angle for 3/2,000 white is 0.085 degrees, slightly smaller than that for 1.3/750. Therefore, it is very likely that the isopter for 3/2,000 white extends to somewhere between 28 and 40 degrees.

To the Editor:—Several years ago Dr. Max Chamlin was kind enough to allow me to observe his methods in New York. I have always been very appreciative of Dr. Chamlin's efforts. He gave unsparingly of his time and knowledge. At the time Dr. Chamlin was using a single target on a paddle, such as he has described in an article. I do not recall his using more than one target on a paddle.

A few years ago when I was attempting to find a technique of testing for visual extinction with standardized targets, I utilized Dr. Chamlin's paddles and used multiple targets on the paddles. From this it was only a short step to using it with the tangent screen. When I scanned the literature in preparation for writing my paper, I went through several articles and also went through the article mentioned by Dr. Chamlin. I missed his reference to multiple targets on a single paddle. I probably missed it because it occupies the last few paragraphs of a relatively long article.

In the article, Dr. Chamlin states that two targets can be used on a paddle but "separate holders are probably better." Further on he states, "This method of simultaneous stimulation shows promise of becoming very useful in eliciting minimal defects but I have not yet studied it fully enough to present any cases at present." Dr. Chamlin does not include any mention of the multiple targets in his own summary of his article.

On the basis of Dr. Chamlin's 1949 article I am perfectly willing to yield priority to him. Suffice it to say, I think the method is a good one. The method is not discussed in three recent textbooks on perimetry (Scott-Traquair, Zuckerman, and Harrington) and deserves publicity.

Regarding the discussion of target size to use, as I said in my article, it is very obvious that the visual acuity of the subject will determine the size of the target used. Unfortunately, I found that with very small targets, 0.5 mm. or 1 mm., the number of confusing responses is vastly increased. Certainly one can use the smaller targets on some patients, and they are very valuable, but for routine checking as part of a screening technique, the use of the slightly larger targets will confuse the patient and examiner less often.

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OPHTHALMIC PLASTIC SURGERY: DEMONSTRATIONS AND DISCUSSIONS, WITH SPECIAL REFERENCE TO ENUCLEATION AND EVISCERATION

Evisceration. WENDELL L. HUGHES, M.D.

Of recent years, especially since the rise and fall of the use of open-faced integrated implants, there has been a great increase in the popularity of evisceration as compared to enucleation. At a meeting of the Committee on Prosthesis held in connection with the American Academy of Ophthalmology and Otolaryngology, evisceration was voted the procedure which gave the best postoperative results by about nine to one.

The indications for evisceration or enucleation and the potential dangers of evisceration are common knowledge (before an audience of this nature), but a comparison of the mechanics involved in the different procedures might prove useful. Inasmuch as simple enucleation is seldom performed in this country and simple evisceration is usually a procedure one is forced to use on account of infection, I will not consider them for the purpose of this presentation. When an enucleation is performed the conjunctiva, muscles, and fascia are of necessity stretched forward if some type of implant is used. The shortening of the conjunctival lining of the socket thus produced tends to pull on the fornices, thereby producing a shallowing of the socket. Shallowing of the fornices is particularly noticeable horizontally and is aggravated by the pulling forward of the fascia bulbi and muscles with the attachment of the check ligaments. On account of this shallowing, or flattening, of the fornices, there is insufficient room for the artificial eye to rotate, and thus movement of the eye is materially limited. The shape of the posterior surface of the artificial eye or buried implant matters only slightly if the margin of the prosthesis is obstructed in its excursion and cannot rotate freely.

The incorporation of a magnet in the implant should permit greater movement if the artificial eye is unrestricted. However, from practical standpoints I have seen very little improvement in the motility of the eye in cases in which a magnetic implant is inserted, as compared with the nonmagnetic implant. If some means of deepening the fornices can be achieved, considerable increase in the range of motility of the prosthesis will result. Usually the range of motility of an artificial eye after enucleation is better temporally than medially because the medial check ligament is frequently tightened by pulling forward more than the lateral. In some cases where the upper fornix has not been foreshortened the upward movement of the eye is fairly good. Likewise when the lower fornix is deep and is pulled downward by its attachment to the tissues acted upon by the inferior rectus, downward movement of the eye is not restricted.

It is generally conceded that motility is better after routine evisceration than enucleation. Considering the afore-mentioned factors, particularly the depth and freedom of the fornices, the deeper the fornices and the better they move with the recti muscles, the more responsive the artificial eye will be. The retention of the depth of the upper fornix in evisceration with intraocular implant partially accounts for the absence of sinking of the upper lid which occurs so

frequently after enucleation. Another factor in this is the support made possible by close fitting of the artificial eye onto the greater convexity of the globe. A third factor is that the artificial eye itself is less bulky than the eye fitted after enucleation. The good support of a thin shell eye accounts also for the absence of stretching effect on the lower lid seen after enucleation, especially in older people where the lower lid often stretches and the lower fornix becomes shallow. Not infrequently the artificial eye slides out. After enucleation the weight of the artificial eye is borne almost entirely by the lower lid. If the lower lid is held down, the eye falls out. After evisceration a properly fitted eye will stay in place even if the lower lid is pulled down away from it.

There are two main types of evisceration with implant, namely, the type in which the cornea is excised and the type in which the cornea is preserved. When the cornea is excised the incision is usually extended into the sclera horizontally or otherwise to allow room for the insertion of an intraocular implant. Even some additional sclera is frequently removed in planning an overlapping closure of the scleral envelope. By making an incision of sufficient length posteriorly in the sclera it is possible to put in a larger implant than is feasible otherwise. The conjunctiva is closed over the scleral closure. In this procedure there is shortening of the anterior portion of the globe and thereby a pulling forward of the site of the muscle insertion. This has somewhat the same effect, although less, on the depth and flexibility of the fornices as in the enucleation technique. Preservation of the depth and freedom of the fornices is best accomplished by the type of evisceration in which an intraocular implant is inserted within the sclerocorneal envelope without excision of any of the anterior part of the eye. There is minimal change in the shape and size of the eye, the normal relations of the muscles to the globe, and the secondary fascial attachments to the fornices.

In the following technique, the conjunctival sac is not foreshortened and the surgery is confined to the upper fornix where it has the least undesirable effect. In fact, when the eye has healed after surgery it is almost impossible to see any sign of surgery having been done. The only result of the surgery is a slight decrease in the size of the globe which allows for the insertion of a very thin shell prosthesis with a concave posterior surface without producing the appearance of exophthalmos.

A description of the technique, which was shown in a film, follows:

Technique.—A transverse conjunctival incision 2 cm. long is made over the insertion of the superior rectus muscle. An identifying 00000 nonabsorbable surgical (silk) suture is placed in the tendon, and it is detached cleanly at the sclera. A transverse scleral incision is made about 2 mm. above the superior rectus insertion almost 180 degrees around the upper part of the globe. If this incision is extensive enough the contents of the globe may usually be removed in one piece for a satisfactory pathological examination. A fairly long reverse-curve cyclodialysis speculum may be used to break the ciliary body attachment to the scleral spur around the inside of the limbus. Then, with a medium-sized bone curet passed around just outside of the choroid, the entire choroidal envelope may usually be removed in toto with the vitreous, iris, and lens in situ.

The entire interior of the scleral envelope may then be inspected with a transparent tampon speculum * for any remaining uveal tissue, particularly around the nerve head. The corneal portion is everted, carefully inspected, and cureted thoroughly to scarify it. The implant is then inserted into the scleral envelope. Three double-arm 0000 absorbable surgical (gut) sutures are then placed from-within-out in the posterior scleral margin and brought forward to pass

* Made by Fritz Gordon Laboratories, Detroit. Originally designed for use after enucleation for inspecting the cut end of the optic nerve.

through the anterior scleral portion about 4 mm. from the margin to produce an overlapping closure. The two side sutures are tied and cut, and one knot is tied in the central suture, which is just anterior to the superior rectus insertion. Each end of this suture is then brought through the superior rectus near the cut end and tied to reattach it. The black silk identifying suture in the tendon is removed and the conjunctival incision closed with a running mattress suture. The corneal surface is cureted thoroughly to scarify it and reduce its sensitivity. A conformer is not used. Dressings are kept on for about three weeks, changed at five- to six-day intervals, and at the end of four weeks an artificial eye may be fitted. This should be a very thin shell, and the posterior surface should be concave throughout to fit the globe accurately without undue pressure any place, particularly in the corneal area. There should be no discomfort from the eye as it hugs the globe underneath. There is less secretion than after enucleation, and the prosthesis can usually be left in for a week at a time. It should be taken out once weekly for cleansing.

The motility and general cosmetic result is considerably better wilth this type of evisceration because the fornices are not foreshortened as in enucleation or in evisceration with removal of the cornea. It allows more room for the margins of the prosthesis to rotate. The upper lid is also supported much better to avoid any depression of the upper part of it, and there is little or no pressure on the lower lid.

Complication.—Extrusion of the intraocular implant is almost impossible because of the four-layer overlapping closure. The scleral envelope is overlapped, the superior rectus is reattached. The overlapped anterior scleral layer and the conjunctiva is closed over that. No conformer is used, as it might cause a necrosis of the cornea by pressure between the implant and the posterior surface of the conformer. Furthermore, since the fornices are not foreshortened, there is no necessity for using a conformer. Sympathetic ophthalmia, leaving remains of an intraocular tumor, or spreading infection posteriorly to the cavernous sinuses or meninges are possible in ill-chosen cases. Pressure dressings used afterwards prevent swelling and any displacement of tissues from that cause.

Contraindications.—There are definite contraindications for this procedure:

1. Presence of a healed limbal or retrolimbal scar over two or three weeks old in which the ciliary body may be incarcerated, because of the possible development of sympathetic ophthalmia.

2. Intraocular tumor (or the likelihood of its presence): Unilateral intractable glaucoma should always be regarded as due to a tumor unless this has been ruled out. Also retrobulbar transillumination should be carried out on the operating table after the conjunctiva has been opened, and if any defect in transillumination is found, tumor should be the presumptive diagnosis.

3. Presence of an intraocular infection, acute or subacute, especially Bacillus pyocyaneus, tuberculosis, and Actinomyces, in which case the incision in the sclera should be left open for drainage and intensive measures taken to combat the infection.

Indiscriminate use of any type of evisceration in place of enucleation should not be considered, but the use of this particular type of evisceration, when it is indicated, will provide a more logical approach. The problem is to provide surgically sound wound closure with better preservation of the depth of the fornices. With a well-fitting artificial shell the cosmetic appearance both statically and dynamically is better than that obtained by any type of enucleation. The normal appearance of the upper lid, the increased motility, and the lack of pressure of the eye on the lower lid are the main advantages. There are definite contraindications which should be observed.

A modification of the original intrascleral implant technique employed by Burch is reported, with a discussion of the technique and advantages.

Comment: Utilizing an Intrascleral Implant

CONRAD BERENS, M.D., and ARNOLD S. BREAKEY, M.D.: Hollow plastic intrascleral implants have been employed after evisceration with corneal excision in 230 cases observed for from 1 to 16 years.

Modifications of the original Rosa-Berens implant and in the technique seemed desirable because of 5 failures in a series of 117 cases. The modified Rosa-Berens hollow plastic intrascleral implant with steel mesh cap and suture grooves, made in adult, juvenile, and infant sizes, was used in 113 cases, resulting in excellent motility and no postoperative complication in one to five years.

Greater motility of the prosthesis is obtained after evisceration, with less enophthalmos and deepening of the supra tarsal sulcus, than after enucleation. Furthermore, a patient more readily consents to the removal of part of an eye than complete removal.

Several ophthalmologists are employing a modification of the Burch technique of retaining the cornea, and, although a larger implant may be utilized to occupy the orbital volume, corneal necrosis has been reported in several cases where the cornea was retained. The fitting of a prosthesis must be infinitely more exacting where the cornea is retained than where the cornea is removed.

Sympathetic ophthalmitis was not observed in this series of 230 cases or in over 400 cases reported in the literature, with or without retention of the cornea.

Both methods afford excellent motility and a near normal appearance, and where indicated, evisceration should be employed in preference to enucleation.

DR. WENDELL HUGHES: Where a choice is possible between evisceration and enucleation, the former is becoming more popular because of better subsequent cosmetic appearance of the artificial eye. The preservation of the normal depth and movements of the fornices is the main advantage of the evisceration technique in which the cornea is left intact. A technique of evisceration which is a modification of that originally reported by Burch is presented, whereby an implant is inserted inside the eviscerated globe through a transverse scleral incision above the cornea. The superior rectus is detached and the incision made above the level of its insertion. The scleral wound above is closed by overlapping and the superior rectus reattached over the line of incision to aid in closure. Evisceration with intrascleral implant is contraindicated after a healed injury through the ciliary body and where an intraocular tumor or infection is present.

Discovery of Malignant Melanoma of Choroid After Evisceration: A Case Report.

BYRON SMITH, M.D., and DAVID B. SOLL, M.D.

The purpose of this report is to record the study of a case in which the diagnosis of malignant melanoma was established by histological study of the eviscerated globe contents.

A Caucasian man, aged 64 years, noticed the gradual onset of diminished vision of the left eye in April, 1958. One month later, he was advised by an ophthalmologist to use drops in the left eye for the treatment of glaucoma. The regular use of the prescribed medication was carried out; however, the visual acuity of the left eye continued to decrease, and the eye became congested and painful. The patient was first observed by us on June 1, 1958.

The vision in the right eye was 20/70 and correctable to 20/20. The right eye exhibited no internal or external abnormalities, except for a few small, pigmented areas on the iris. The patient advised us that these pigmentations had not changed in size, shape, or color. The visual field, gonioscopy, and tension of the right eye were normal. The cornea of the left eye was steamy in appearance. The conjunctiva and episcleral tissues were congested. The left pupil was partially dilated and fixed. The iris vessels were dilated. Numerous keratic precipitates were scattered over the lower half of the corneal endothelium. Density and edema of the cornea prohibited

the identification of floating cells in the anterior chamber. The angle of the anterior chamber was so shallow that gonioscopy was nonrevealing. The lens was edematous and opaque. The ocular tension was 60 mm. Hg (Schiøtz). Anterior transillumination failed to reveal any variation in density.

A diagnosis of absolute glaucoma of unknown cause was made by us. The patient was admitted to the hospital for treatment and observation. Physical examination, laboratory studies, and a series of x-ray films provided no diagnostic signs of neoplasm. Radioactive phosphorus studies were not carried out. Antiglaucoma medication failed to normalize the ocular tension or eradicate the pain.

In view of the failure of medical treatment and in consideration of statistical evidence that 4% to 11% of blind eyes with opaque media contain malignant melanomas, histological analysis of the ocular contents was advised.

Under general anesthesia, on June 4, 1958, an incision was made through the conjunctiva and sclera, parallel to the equator of the globe in the upper nasal quadrant. A long cyclodialysis spatula was inserted to free completely the uvea from its scleral attachments. The incision was then extended parallel to the equator from three o'clock to nine o'clock, anterior to the insertion of the rectus muscles. The uveal tract and its contents were removed in one piece and sent to the laboratory for immediate study. After thorough curettage of the internal surface of the sclera, an 18 mm. plastic sphere was inserted. The sclera was closed with a continuous suture of 0000 chromic catgut.

Twenty-four hours later, the laboratory reported that the globe contents contained a dense, dark, firm mass histologically characteristic of malignant melanoma. The predominant cell type was of an epitheloid nature.

Forty-eight hours after evisceration, enucleation was performed under general anesthesia. The conjunctiva, including the wound, was removed along with the sclera. An implant was not used because it was felt that a more accurate postoperative follow-up would be possible in the absence of a surgically placed foreign body. Tenon's capsule was closed with four chromic catgut sutures. The conjunctiva was closed with 000000 chromic catgut sutures. The postoperative course was uneventful. The patient was discharged from the hospital on the seventh postoperative day.

Histological study of the optic nerve and Tenon's capsule showed no evidence of neoplastic disease. The scleral shell showed no microscopic evidence of malignant melanoma.

Three weeks after surgery an artificial eye was fitted to the socket. Repeated examinations have disclosed no evidence of recurrent disease. Radioactive phosphorus (P^{32}) uptake studies, done on Nov. 5, 1958, showed 24% the first hour, 27.3% in 24 hours, and 28.2% in 48 hours. The series of x-ray films taken on the same date were reported as normal. The laboratory considered the report of the radioactive phosphorous uptake studies essentially negative. Test for melanin in the urine was negative.

Wilder and Paul (*Mil. Surgeon* 109:370, 1951) reported a statistical study of longevity after enucleation for malignant melanoma. Eighty per cent died within five years. Dunphy (*Am. J. Ophth.* 44:313, 1957) reported an over-all mortality of 48% within five years after enucleation for malignant melanoma. Westerveld-Brandon and Zeeman (*Ophthalmologica* 134:20, 1957) conclude from their studies that the prognosis of malignant melanoma of the choroid in persons beyond the age of 60 is so poor that enucleation is of questionable value. In a series of 210 cases studied by Wilder and Paul, it was concluded that the prognosis in malignant melanoma exceeding 1,300 cu. mm. in size is more grave than it is in tumors of a smaller volume. The outlook in malignant melanomas of the spindle-cell type is better than it is in tumors exhibiting a predominance of epithelioid type cells. Reese (cited by Saunders, *Tr. Am. Ophth. Soc.* 50:375, 1952) has stated that

cases showing extrascleral extension prior to enucleation rarely develop orbital recurrence. His opinion is in accordance with others who believe that malignant melanoma cells gain entry into the circulation at an early stage of the disease. Metastatic growths are dependent upon the ability of the cells to undergo independent growth. The character of the cell is the determining factor, rather than the mere presence of the tumor cells in blood or lymphatic fluids. Metastatic growth of a malignant melanoma has been reported to occur as late as 36 years after enucleation. Newton (*Am. J. Ophth.* 21:668, 1938) reported a case in which local recurrence occurred 14 years after enucleation.

The prognosis in this case, five months after surgery, appears optimistic, if one considers the present physical findings only. An age beyond 60 years, the tumor volume of greater than 1,300 cu. mm., and the epithelioid type cell militate against a favorable prognosis in this case.

The influence of surgery upon the prognosis is more dependent upon the character of the tumor than it is upon the operation itself.

It is our hope that this case report will stimulate surgeons to request early examination of the contents of an eviscerated globe. The absence of tumor in the sclera and optic nerve brings forth the question of the possibility of complete removal of malignant melanoma of the choroid by evisceration. In our opinion, the relative infrequence of malignant melanoma of the choroid and the questionable value of enucleation should encourage enthusiasm in a surgeon who prefers to do an evisceration instead of an enucleation in the apparently uncomplicated case.

In our experience, the most satisfactory means of acquiring the optimum cosmetic result is preservation of the cornea, evisceration, and intrascleral implantation of a sphere.

Discussion

DR. CHARLES A. PERERA: It looks as if the type of surgery done would have no effect on the prognosis of this patient, which is somewhat guarded, in any event. It seems evident from Dr. Smith's study and from the literature that if there are metastases they are not related to the enucleation or evisceration but are the result of tumor cells which have escaped into the blood stream and have become implanted in different parts of the body where they may or may not survive.

Enucleation—Recent Trends. RICHARD C. TROUTMAN, M.D.

I have been asked to comment on recent trends of enucleation surgery. At the moment, however, enucleation seems to be relatively unpopular. This is especially true of our present group with the possible exception of our discussor, Dr. McLean. I am reminded of a recent discussion at the American Academy of Ophthalmology and Otolaryngology during which one of our prominent eye-makers stated, when asked his opinion of the best *enucleation* technique, "We seem to have come the complete circle from gold ball back to gold ball again." On a superficial examination of this problem this statement would seem to be true. Most eye surgeons, who within the last 15 years radically changed their approach to enucleation surgery, have reverted to our earlier less complicated procedures. In most instances they have completely given up their efforts to obtain any form of positive integration of the implant with a prosthesis. At the present time it appears many have given up enucleation in a large percentage of cases in favor of evisceration. Other equally competent eye surgeons have refused for various reasons to have anything to do with the new implants at any time and have continued with simple enucleation technique. These are among the most fortunate of men, considering the problems that have arisen for those of us who have experimented in this field.

About seven years ago, when the fever for implant surgery was running high, a symposium on implants and enucleation techniques was held at the American Acad-

emy. A number of us participated in this program. Among the group were Dr. Hughes and myself. We went to great lengths to show the advantages of the new implants, both of the integrated and buried types. My assignment was a national statistical survey of the use of the new implants, which, taken in light of our present-day thinking, should have taken us up short in 1951 and made us reevaluate our position. However, we were too much carried away with ourselves and our immediate results to consider reevaluation. Even if we had, it is doubtful that we would have been able to convince the majority of ophthalmologists that they should not continue these techniques. Consequently, over the past seven years, numerous implants have been devised, all of them a variation of the basic theme originally set by Dr. Cutler and Dr. Ruedemann. None of them employed any startingly new principles of lasting importance. All of them were essentially surgically unsound seen in the light of the eventual problems they caused.

In my opinion, however, all of the blood, sweat, and tears of the doctors and the prosthesis-makers and, last but not least, the patients were not in vain. First, I think enucleation has been established as a surgical procedure on a par with many of our intraocular operations. Today when the ophthalmic surgeon approaches the case for enucleation he must consider not just removal of the eye but also the eventual cosmetic result to be enjoyed by the patient. To this end he exercises far more care in the selection and execution of the enucleation or evisceration procedure than he did prior to the age of the integrated implant. Second, the patient himself has been made aware of the cosmetic problems to be encountered after the removal of the eye. He in turn demands a better cosmetic result because he suspects it can be obtained. He also demands that the ophthalmologist and the eye-makers cooperate during the postoperative period until a satisfactory result is obtained. Third, the ocularist (eye-maker), by reason of his having worked more closely with the ophthalmologist during this period, has become more cognizant of the problems of the ophthalmologist, just at the ophthalmologist has become more aware of the problems of the ocularist. He has been forced, albeit willingly, to improve his techniques in the production and fitting of eyes. He has come to practice more appropriate sterile techniques in his office through his close association with the ophthalmologist. It was not uncommon in the past for a patient who had had an eye removed to be referred to an ocularist and never to be seen again by his ophthalmologist. I dare say that this is seldom true today. Because of this trend the ocularist has gained new stature in our profession, and because of this he becomes a more valuable adjunct to our total management of the patient. This has recently been demonstrated by the formation of the Society of Ocularists, now recognized by the American Academy of Ophthalmology and Otolaryngology, and by their participation in greater numbers in the commercial and scientific exhibits of the various ophthalmological meetings.

It is difficult to discuss *recent* trends of enucleation surgery without going back to their origin to some extent. Enucleation has been with us as a recognized ophthalmic surgical procedure since the latter part of the 19th century. Both of the operations in common use today were devised at that time. Enucleation has enjoyed such a lowly position in ophthalmic surgery that no attempt was made to change these techniques until just prior to the Second World War. At that time Drs. Cutler and Ruedemann, the fathers of modern enucleation surgery, introduced, respectively, the Cutler-Basket Implant, which is the prototype of today's buried integrated implants, and the whole eye restoration of Ruedemann, which is the prototype of the now-discarded exposed integrated implants. One other innovation was introduced by myself in 1949, in the integrated magnetic implant. This was an attempt to provide by means of magnetic attraction the advantages of both the buried integrated implant and the ex-

posed integrated implant with positive connection between the prosthesis and the implant. All of these implants were attached by some means to the extraocular muscles. The 1951 survey showed that 27% of all exposed integrated implants of the basic Ruedemann type were extruded or removed within five years. At the present time, though no accurate survey has been made, personal communications indicate that less than 10% of these implants still remain with the patients. The Academy survey indicated that the buried integrated implants extruded in 10% of the cases. This rate of extrusion has mathematically increased, and again, though there are no accurate statistics, personal communications indicate at least 25% have extruded or have been removed. In the case of the buried integrated implant, these statistics do not, in my opinion, have the same significance as the extrusion rate of the exposed implants. Many buried integrated implants have become exposed owing to poorly fitting prostheses. As we shall see, fitting is a critical factor in this type of socket. Once exposed by pressure necrosis as a result of poor fitting technique, the once-buried implant follows the natural course of the exposed implant to extrusion or removal. If a buried integrated implant can be properly fitted with a prosthesis, one should have no higher extrusion rate than with a buried spherical implant. This is very well illustrated by the Allen implant, which has been used probably more extensively than any other single implant. At the State University of Iowa, where Mr. Lee Allen fits all Allen implants, 95% of these implants are in socket and working well. In my own hands, however, where the making of prostheses is not under such close control, 15% have been extruded or removed. There remains a vast job in educating the ocularist in the fitting of buried integrated implants. Unfortunately, though their numbers are small, their traditional differences are so great that a coordinated program has been difficult to bring about. This, however, is being implemented next year by courses within the instruction program of the American Academy, to which all ocularists will be invited to learn the new fitting techniques.

In my opinion the greatest advances in enucleation *surgical* techniques are the following:

1. The more careful dissection of the orbit with accurate localization of muscles; the accurate dissection of the optic nerve and the use of the *snare* for sectioning.

2. The positive attachment of the muscles to the implant or through the implant to each other, preventing migration of implants and facilitating motion.

3. The more accurate dissection of Tenon's capsule and conjunctiva with layered closure of these structures, so as to afford maximum restoration of the cul-de-sac.

4. The use of implants with better volume relations and shapes designed to enhance motion of the prosthesis.

The most important advances in implants and prostheses are the following:

1. New materials which are inert in body tissue, such as methyl methacrylate, polyethylene, tantalum, and stainless-steel mesh and clips. These are easily molded and worked, making possible new shapes and combinations of materials heretofore impossible.

2. The flattened anterior face of many implants, which, when fitted with a matching prosthesis in an ample socket, greatly increases the motility.

3. The plastic artificial eye, which permits new shapes necessary to fit these new implants and which is more lifelike and durable.

4. Socket-molding techniques which give the ocularist an accurate guide to socket shape and greatly aid in fitting the new flat-faced implants accurately.

These advances have yet to be embraced by all with special reference to the fitting techniques. No attempt is made in most instances to confine spherical implants permanently to Tenon's capsule. In addition, since the implant is not attached to the extraocular muscles, it can and does become displaced between the muscles into another

area of the orbit. This often results postoperatively from improper fitting of the Snellen or reform prosthesis, which after months or years of wear gradually shifts position. Once this has occurred, the prosthesis is no longer cosmetically desirable and must be removed and replaced with another. The new eyes tend to be too small for good cosmetic effect or poorly shaped. If used in sockets with integrated implants, a prosthesis of the Snellen type cannot push the implant into another part of the orbit. Erosion, therefore, occurs at the pressure point(s), and secretion accumulates in the dead spaces. Ocularists are in many instances unaware of the type of implant fitted, since the surgeon, who should have great interest in this problem since he has performed the surgery, does not bother to inform the patient or the ocularist of the size or type of implant. (Most stocks of artificial eyes are made in the same basic shapes as the old glass Snellen reform eye. These are eminently unsuitable for use with buried integrated implants. They are even unsuitable in many instances for use with spherical implants, since they do not exert even pressure on socket structures and also have dead spaces which allow secretions to accumulate and become infected.) The use of new socket-molding techniques gives the ocularist a guide to socket shape. It permits him to design his prosthesis in plastic to fit the socket, so as to eliminate pressure points and dead spaces. The ophthalmologist should demand, where economics and qualified personnel permit, that his patient, no matter what type of implant he wears, be fitted with an eye in plastic designed through use of a socket mold.

It is my opinion that the sphere may still be the most satisfactory implant for the average ophthalmologist, since it gives a minimum of operative and postoperative problems. If he wishes to improve his cosmetic results, however, and is willing to go through the trouble of working with a competent ocularist actively, he can obtain a much improved and more lasting cosmetic and functional result by using one of the newer buried integrated implants attached to the extraocular muscles. Before he does this, however, he must be well acquainted with the capabilities of his ocularist and should insist upon knowing the experience the ocularist has had in fitting these special prostheses.

One of the reasons for the present popularity of the evisceration technique, especially that technique which retains the cornea, is that the ocularist may be skilled in fitting contact lenses. This technique provides for a perfect fit of the socket by the prosthesis and affords a maximum cosmetic result with a minimum of postoperative problems from secretion because of the almost complete elimination of dead space. Motility is increased because the prosthesis is closely applied to the globe and remains in position on the globe. Superior lid sulcus is prevented because an adequate-sized implant is positioned well forward in the orbit and cannot be moved out of its position. An evisceration procedure essentially is an integrated buried implant, since it fulfills all of the requirements of the technique, except careful dissection of the orbit, which is not necessary. It allows for placement of a maximum-sized implant with ideal volume relation —best about 18 mm.—and provides a strong envelope attached to extraocular muscles so that the implant is retained in the ideal orbital position. I do not wish to steal any of Dr. McLean's thunder; however, one of the greatest arguments against this technique is that it destroys pathological material, and, as Dr. Smith has pointed out in his case report, one may inadvertently encounter an intraocular tumor in the course of evisceration. Again evisceration is essentially an intraocular operation and along with this should go approximately the same number of sympathetic ophthalmias one sees in the course of our standard intraocular procedures. Therefore, one should have in his armamentarium a good enucleation technique which provides the patient with almost as good a postoperative appearance as can be provided by the evisceration technique and will involve a minimum

of fitting problems. The implant used should not exceed the capabilities of the ocularist or the ophthalmic surgeon in question. For this reason, I still advise that the majority of enucleations be done with the spherical implants and only where circumstances permit should buried integrated implants be used. Evisceration technique, however, is simple enough and the fitting techniques well enough established by most ocularists that this procedure can be used as a substitute when feasible for enucleation with spherical implant or as a substitute for enucleation with integrated implant.

I should like to show as an example of a good buried integrated implant that of Dr. Braley and Mr. Allen of Iowa. Their operation and implant appear at the present time to have the most promise of being the choice for buried integrated implant. I am not completely satisfied at the moment with the performance of my superior rectus tunnel implant and will not advise its general use until more experience is obtained. The original Allen implant has been proven in practice, and, though there are some problems with this original model, I would consider it preferable at the moment to the latest design. The operative technique and initial statistical results will be published in the near future for those of you who wish to try this implant.

Discussion

DR. JOHN M. MCLEAN: I find myself this evening cast in the role of the still small voice of conservatism. I hope it is not entirely a voice crying in the wilderness of evisceration stumps. I undertook this assignment with some hesitation because I do not like to differ with my highly respected and very good friends who have presented tonight the case for evisceration instead of enucleation. However, I feel I cannot stay quiet when only one side of a question is presented. So I shall say a few brief words for enucleation rather than evisceration.

You have all heard the arguments for evisceration presented and illustrated very ably by some of the most enthusiastic eviscerators in the country, but to my mind all of these arguments can be summed up in four small words: somewhat better cosmetic result. Now the case for enucleation has many arguments. I shall take time for only three, two of which have been anticipated by all the speakers of the evening; the third has not been dwelt upon particularly by them. They are, of course, malignancy, sympathetic disease, and the advancement of scientific medical knowledge.

Now for malignancy: it is argued by the eviscerators that the mistake of eviscerating an eye containing a tumor should not be made. If you enucleate, of course, that mistake cannot be made. That it can be made and is made was demonstrated by Dr. Smith this evening and is amply demonstrated by pathologic specimens in various laboratories throughout the country, including the Armed Forces Institute of Pathology. If enucleation of the globe is the best means we have of saving the patient's life and if stirring up a tumor and pushing malignant cells into the blood stream is the best means we have of producing metastases, then the only question we must answer is how often are we liable to eviscerate a tumor-containing eye inadvertently. We are all agreed we do not want to do it on purpose. Though there are no adequate figures, we have some hints. A few years ago, Dr. Bernard Samuels made a study of unselected eyes enucleated for cosmetic reasons, and a surprisingly large number of these contained tumors which were neither diagnosed nor suspected clinically. If those eyes had been eviscerated instead of being enucleated, how many of those patients might have suffered evisceration-death instead of enucleation-life? No one can answer that question, but on the side of conservatism I suggest that you think twice before eviscerating, because of the possibility of tumor. Dr. Hughes has mentioned posterior transillumination as a very important safeguard if you must eviscerate.

Second, the matter of sympathetic disease: certainly we know that sympathetic ophthalmia is produced by a perforating wound

which damages uveal tissue, and what better description is there of evisceration than a perforating wound which damages uveal tissue? Dr. Berens has suggested that he has not found cases of sympathetic ophthalmia in the literature. That is not surprising because, after all, this type of clinical error is not one which stimulates its perpetrator to publish a paper of confession, but cases of sympathetic ophthalmia following evisceration have occurred. Dr. Hughes, one of the proponents of evisceration, told me privately that he is aware of at least two. They did not happen to him, they happened to "Dr. Elsewhere," and they were not cases he would have eviscerated, but they happened. So Point Number Two, in the interest of safeguarding the vision of your patient's remaining eye, think twice before evisceration.

My final point: the advancement of scientific knowledge. You are all aware that much of what we know in ophthalmology today was learned through study in laboratories of enucleated not eviscerated eyes; a study of adequately prepared specimens. Now you have heard this evening that a specimen can be obtained from evisceration; Dr. Hughes has shown you some of his best. This is the best specimen that I could find from an evisceration (slide), and this, though not done by Dr. Hughes, was provided by one of the speakers of the evening. The pathologic report, after describing in some detail this rather disorganized mass of tissue, concludes "no definite diagnosis is possible." I think when you look at the specimen you may sympathize with the man who wrote that report.

The other slide which I would like to show you is one of an enucleated eye. Now the eviscerated specimen was obtained by an evisceration expert, one of the best. A specimen from enucleation can be obtained by the earliest beginner among the residents, and, as you are all aware, it can teach us a great deal from the careful, accurate, anatomic specimen it is. It just so happens in this particular case there was a small melanoma in the choroid, back near the nerve. I do not know whether with an opaque lens or cornea such a small tumor would have been discovered by posterior transillumination or not. I venture to suggest I might have overlooked it. By posterior transillumination the experts might have picked it up, changed their minds, and enucleated rather than eviscerated.

Therefore, in closing, as the voice of conservatism, let me suggest not that you never do evisceration but that before jumping on the evisceration bandwagon you think twice and think hard in the interest of your patient's life, your patient's vision, and the future of the knowledge of ophthalmology as balanced against a slightly better cosmetic result. As the advertising slogan has it, "Don't be half-safe!"

DR. CHARLES A. PERERA: Dr. McLean's comments make it appear that evisceration sounds like a bad word. However, there will be no rebuttal, and I think the audience itself should be the judge and decide as to its preference for enucleation or evisceration. We have in the audience some ocularists, or prosthesis-fitters, and I wonder whether any of them wish to add a word. Mr. Bethke, from the Institute of Ophthalmology, might care to say something.

MR. EMIL G. BETHKE: I want to compliment the speakers on having a very good understanding of the eye-maker's point of view; it is gratifying to us in that line of business. In inquiring around, trying to get some information on fitting after evisceration, I was told that a greater amount of ptosis occurred in the eviscerated eye; at least, that was the experience of my informants. I wonder whether Dr. Hughes or Dr. Berens has had any experience in regard to this.

DR. WENDELL L. HUGHES: Dr. Berens says he has not seen any, and I do not believe I have either, Mr. Bethke. I do not know what the reason for ptosis would be after evisceration, except that too small a prosthesis was fitted. I do not see why there should be more ptosis after evisceration than after enucleation.

News and Comment

ANNOUNCEMENTS

Courses at The Mount Sinai Hospital.—Columbia University is sponsoring the following courses at The Mount Sinai Hospital, New York:

"Gonioscopy and Tonography," by Drs. Sylvan Bloomfield and Jules Yasuna, during October, 1959.

"Ophthalmoscopy for General Practitioners and Pediatricians," by Dr. Robert Coles, during November, 1959.

"The Schepens Binocular Indirect Ophthalmoscope and Its Use," and a discussion of the indications for the various operations for the cure of detached retina. This course will be given by Dr. David Silver during December, 1959.

For complete information in reference to the above courses, inquiries should be directed to the Registrar for Post-Graduate Instruction, The Mount Sinai Hospital, 1 E. 100th St., New York 29.

Symposium on Pleoptics in the Treatment of Amblyopia.—On Sunday, Oct. 11, 1959, at 8 p. m., the Annual Joint Meeting of the American Orthoptic Council and the American Association of Orthoptic Technicians will be held in the Waldorf Room of the Conrad Hilton Hotel. The subject of the meeting will be a Symposium on Pleoptic Treatment of Strabismic Amblyopia. Papers on the pathophysiology, diagnosis, and therapy of strabismic amblyopia, especially of amblyopia with eccentric fixation, will be presented by Drs. Gunter K. von Noorden and James E. Miller and by Misses Geraldine L. Wilson and Nancy M. Capobianco. Hermann M. Burian, M.D., will be the moderator. There will be a question and answer period at the end of the presentations. Anyone wishing to submit written questions is urged to send them ahead of time to Hermann M. Burian, M.D., Department of Ophthalmology, University Hospitals, Iowa City, so that adequate answers may be prepared by the panel.

PERSONAL

Dr. Albert E. Sloane.—Dr. Albert E. Sloane, of Boston, established a Low Vision Clinic in the eye department of the Mayer de Rothschild Hadassah University Hospital, in Jerusalem, in September, 1958.

CORRECTION

"In the article entitled, 'An Isopter in the Intermediate Field of Vision,' published in the April, 1959, issue on page 130, the following three corrections should be made: (1) In the legend on Figure 1, the phrase 'width of fixation on bowl' should actually be 'point of fixation on bowl.' (2) In the same legend, '642 mm.' should be '1300 mm.' (3) In the legend on Figure 4, the word 'arc' should be replaced by the word 'one'."

Books

Acta. First Afro-Asian Congress of Ophthalmology, incorporating the Bulletin of the Ophthalmological Society of Egypt, Vol. 51, 1958, Cairo, Egypt.

The first Afro-Asian Congress of Ophthalmology was held in Cario, March 5, 1958. The Acta, which is the published account of the workings of the Congress, resembles in makeup that of the International Congress of Ophthalmology. In the 734 pages the administration and list of members are given. The statutes and meetings of the Council are reported, together with the meetings of the General Committee and the opening and closing ceremonies. The complete program of the Congress is presented in English and a résumé in Arabic, English, and French. Some of the discussions are also included. The main subjects were trachoma and the acute ophthalmias. Five symposia were held on glaucoma, cataract, atomic energy, endemic diseases of the Middle and Far East, and injuries of the eye. There were thirty-nine free papers. The printing and paper used are excellent, but the illustrations are only fair: they range from a few excellent ones to those which should never have been published, as they show nothing at all.

As would be expected, the Afro-Asian Congress is composed of members from the United Arab Republic, Ceylon, India, Indonesia, Iraq, Jordan, Lebanon, Saudi-Arabia, Sudan, South Africa, Tunis, Thailand, and Turkey. In addition, the U. S. S. R. and the People's Republic of China were not only in attendance but contributed heavily to the program. Surprisingly, there are two members included from the Philippines. There is an obvious absence of anyone from the Western world in either the membership or the program for free papers.

The majority of the papers are well done, and there was a reasonable amount of discussion. It is interesting to see that the Russian, Prof. Eroshevsky, gives Grossfeld, Mashkovsky, Thygeson, Richardson, et al. credit for having established the stimulating agent of trachoma as a virus and, in his paper on goniopuncture and congenital glaucoma, credits Scheie as the first to propose the operation of goniopuncture. Eroshevsky finds the results of goniopuncture satisfactory and regards it as a useful procedure.

On the other hand, there is the constant emphasis on national credit rather than personal credit in many of the articles. Although most of the world divides trachoma into four stages, the last of which is admittedly not true trachoma, and attention has been drawn to this frequently in our recent literature, Eroshevsky states, "In contrast to the other schools, the Soviet School divides trachoma into four stages. . . ." "There is a fourth stage of trachoma which, properly speaking, cannot be considered as such." "In these last years the treatment of trachoma in the U. S. S. R. took a different direction. On the initiative of Professor Chumakov numerous observations were carried out in treating trachoma with new antibiotics; chloromycetin and sintomycin. . . ." "I cannot pass in silence over the prophylactic fight of trachoma carried out by the service of Public Health in the Soviet Union." "The Soviet School shares other schools in considering the antibiotics valuable elements in the treatment of trachoma." "The author describes the methods of prophylaxis of trachoma in the Soviet Union."

It is presumed that either love of country or pressure from outside must induce these Russian authors to pay continual obeisance to the flag; it seems strange and lamentable to find flag-waving in a humanitarian field.

History of Ophthalmology. By George E. Arrington Jr. Foreword by Felix Marti-Ibanez. Price, $4. Pp. 174, including index. MD Publications, Inc., 30 E. 60th St., New York 22, 1959.

This little book on the development of ophthalmology from prehistory to today makes delightful reading and serves as a useful orientation for those who

are teaching. There are short chapters on the contemporary acceleration of ophthalmic technology, contemporary medical concepts in relation to ophthalmology, and an evaluation of current trends anticipating the future. The author points out that while ophthalmological teaching today is generally aimed at producing "safe ophthalmologists," the student should also be stimulated to be dissatisfied with the very techniques which he is taught to use in order to better them. He should also be taught "the heritage of ophthalmic science within civilization, in order to inspire his respect for the stature of the specialty and his aspirations to further its role in medicine and society."

System of Ophthalmology: Volume I. The Eye in Evolution. By Sir Stewart Duke-Elder. Price, $27.50. Pp. 853, including index, with 902 illustrations, 15 color plates, and 350 marginal illustrations. The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, 1958.

In a characteristically British understatement Sir Stewart starts the preface of this volume with the following words: "The reception accorded to by textbook of ophthalmology has persuaded me that there is a need for its continuation in a second edition." The first four volumes of what is undoubtedly the greatest English text in ophthalmology have long been out of print and, as Sir Stewart says, intentionally so, because they have long been out of date. He has now addressed himself to the task of remedying this defect.

This first volume is an amplification of the first twenty pages of Volume I of the old textbook and has been written by Sir Stewart as a labor of love in the true sense, in that it is a subject in which he is particularly interested. This is somewhat understandable in that it can probably be thought of as the philosophy of ophthalmology. While avoiding the minutiae of anatomy, histology, embryology, physiology, and biochemistry of the eye, it covers the form and function of the eyes as they are found in the animal kingdom. This is demonstrated by the divisions into which the book has been case, as follows:

Part I. "The Effect of Light on Living Organisms." This takes in the effect of light on metabolism, with a consideration of the effects of the cycle of day and night with its rhythm of changes in illumination on living creatures. A chapter is devoted to the effect of light on movement and one to the effect of light on pigmentation.

Part II deals with the evolution of the visual apparatus and starts with the simple invertebrate eye, coming up the scale of the lower vertebrates, cyclostomes, fishes, amphibians, reptiles, birds, and, finally, the eyes of mammals. A separate chapter deals with the central organization of vision.

Part III considers the functions of the eyes of animals and contrasts the vision of the primitive forms with the final emergence of binocular vision in the higher mammals.

Part IV gives consideration to a number of evolutionary by-ways which are indirectly concerned with vision, such as the pineal and the lateral line organs, rudimentary eyes, bioluminescence, and the electric organs of fishes.

The picture of Charles Darwin appropriately occupies the front page. The text is written in Sir Stewart's best style, illustrated magnificently, and with an unusual addition of line drawings in the margins by Sir Stewart's secretary, Miss Rosamund Soley, for whom some extraordinary kudos should be invented, since as Sir Stewart says, "She has typed and prepared the manuscript, corrected the proofs, and undertaken the immense and somewhat thankless task of verifying the bibliographies, prepared the zoological glossary and the index, and drawn the 350 marginal sketches."

Unlike other books which must necessarily remain as reference works, this volume is one to be read by ophthalmologists, and not consulted. It is to be reserved for those moments when, the work of the day over, and with not too tired a mind, the ophthalmologist returns to his basic biological interests, which are necessarily as much a part of him as they are of any physician worthy of the name.

Atlas of the Ocular Fundus. By Prof. Dr. Oswald Marchesani and Prof. Dr. Hans Sautter. Price, $80. 275 illustrations, with 262 in color. Hafner Publishing Co., Inc., 31 E. 10th St., New York 3, 1959.

This is an English translation of the "Atlas des Augenhintergrundes," published by Urban and Schwarzenberg in Munich and Berlin, in 1957. The English translation has been prepared by Dr. A. Philipp, of Llanelly, Wales.

This is a magnificent series of colored illustrations of the fundus oculi made by Mr. Saumer and Mr. Zeltmann at the Clinic in Tubingen. While the cost of the book is high, the plates are well worth this expenditure. They have no equal in the English language.

Most of the conditions described are fairly common, and therefore the book is useful for all students of ophthalmology and should be in the library of every hospital devoted to residency training programs. Occasionally a plate is labeled with a diagnosis which at the best is questionable and does not represent the generally accepted typical picture—for example, Plate 46, entitled "Neuroretinopathia angiospastica"—the picture as shown here is a Grade IV hypertensive fundus and could be that of any of the hypertensive states, including the collagenous diseases. There are very few plates, however, which can be questioned. Each plate is accompanied by a description in English, French, and Spanish.

Both author and publisher are to be congratulated for producing an atlas which so faithfully portrays the pathologic fundus. This is a real contribution to ophthalmology.

Le Diagnostic précoce du glaucome débutant. By R. Weekers, E. Prijot, Y. Delmarcelle, G. Lavergne, M. Watillon, L. Gougnard, C. Gougnard-Rion, and J. Gustin. Price, not given. Pp. 209. Imprimerie Medicale et Scientifique, 67 Rue de l'Orient, Brussels 14, 1959.

Part I of this monograph deals with the fundamental principles of physiology, embryology, and anatomy which are pertinent to the study of glaucoma. The principles of tonometry and tonography are discussed in the light of present knowledge, and methods of studying the visual function in patients with suspected early glaucoma are described.

In Part II of the monograph the authors describe their own clinical approach to the study of patients with various types of glaucoma, both primary and secondary. It is their belief that, for clinical purposes, virtually all glaucoma is the result of a deficiency in aqueous outflow. Ideally, the measure of the resistance to the outflow of aqueous humor would be the method of choice in the diagnosis of early glaucoma. Imperfections in tonographic methods for the measurement of outflow, however, prohibit its use to any great extent in clinical practice.

Tonometry remains, according to these authors, the best single method for determining the presence or absence of glaucoma. The value of this method depends upon the utilization of a rigorously standardized Schiøtz tonometer, adherence to the calibration table of Friedenwald, and the consideration of factors of ocular rigidity. The authors recommend the aplanation tonometer because it minimizes the effects of scleral rigidity.

Other than tonometry, the authors recommend careful evaluation of papillary excavation and alteration of visual functions. It is their belief that serial photographs of the optic discs may be helpful in determining the presence of progressive excavation. Perimetry is still the best method for determining the progression of changes in visual function.

The authors finally urge routine tonometry in all patients over forty years of age and careful attention to the depth of the angle and to the presence of conditions which may result in secondary glaucoma.

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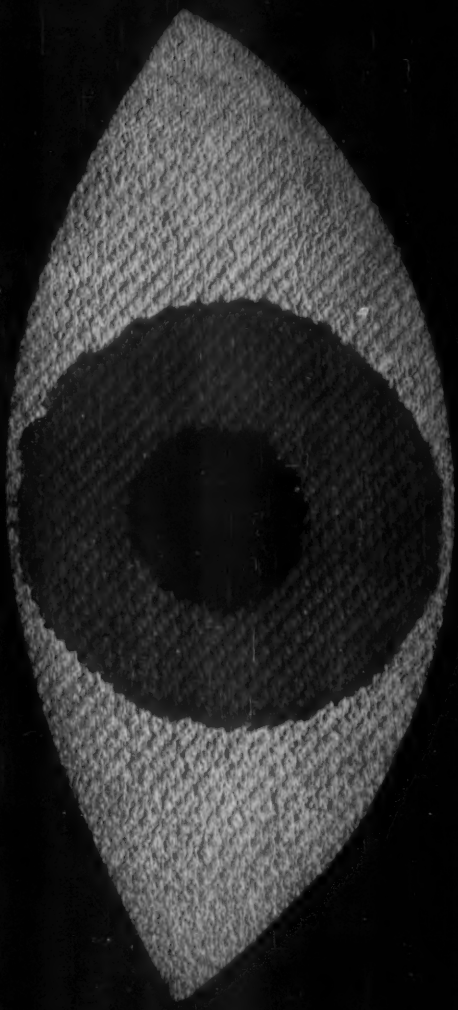

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References: (1) Perkins, E. S.: **Practitioner 178**:575, 1957. (2) Smith, C. H.: **Eye, Ear, Nose & Throat Month. 34**:580, 1955. (3) Blakiston's New Gould Medical Dictionary, ed. 2, New York, McGraw-Hill Book Company, Inc., 1956, p. 945. (4) Ostler, H. B. & Braley, A. E.: **J. Iowa M. Soc. 44**:427, 1954.

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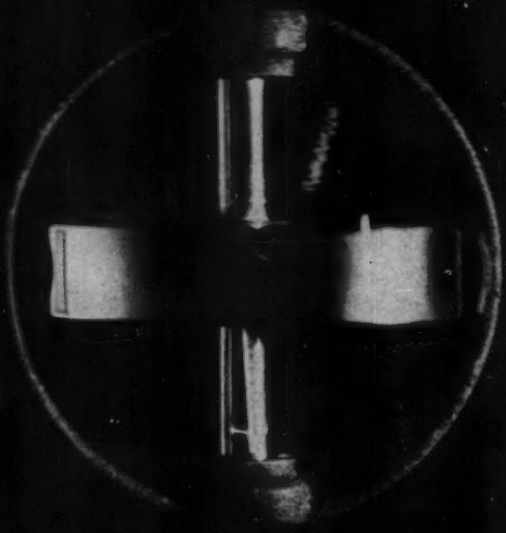

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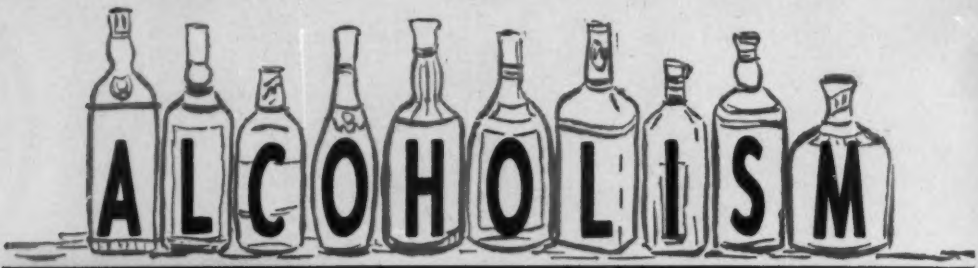

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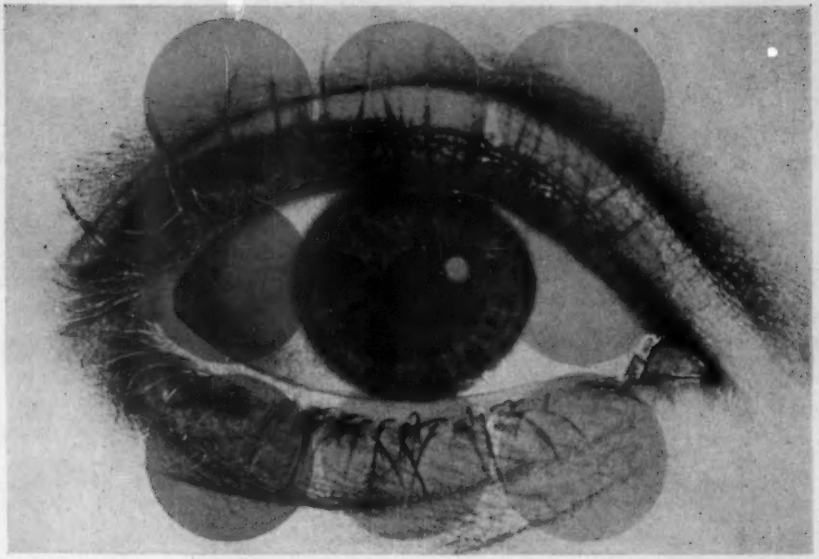

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1. New and Nonofficial Drugs; J. B. Lippincott Company, Philadelphia, 1958, p. 243.

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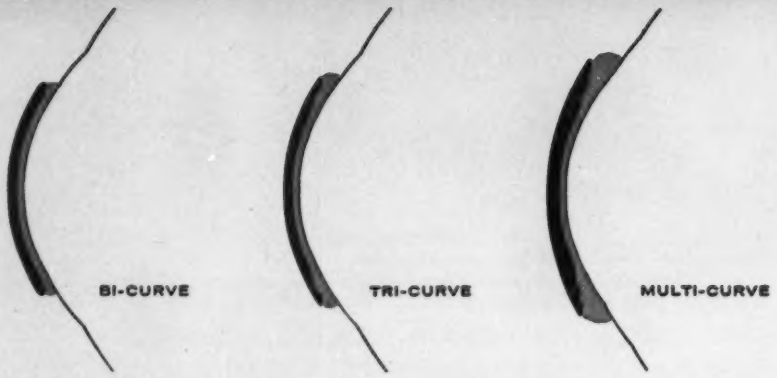

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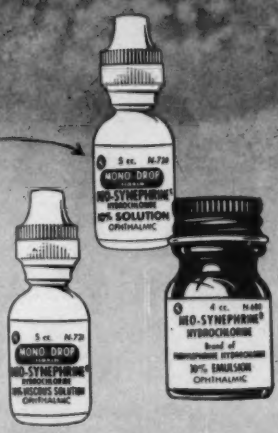

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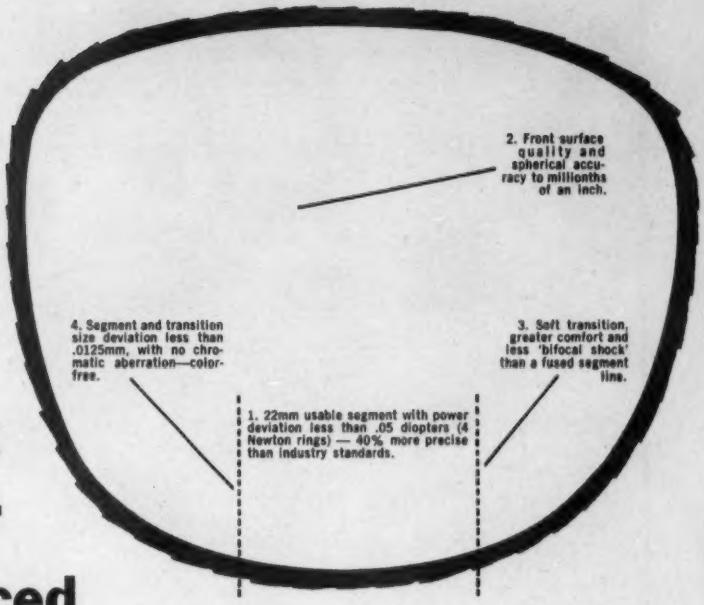
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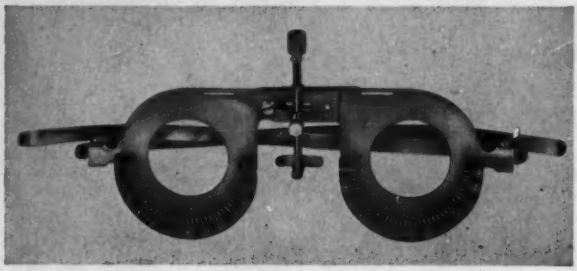

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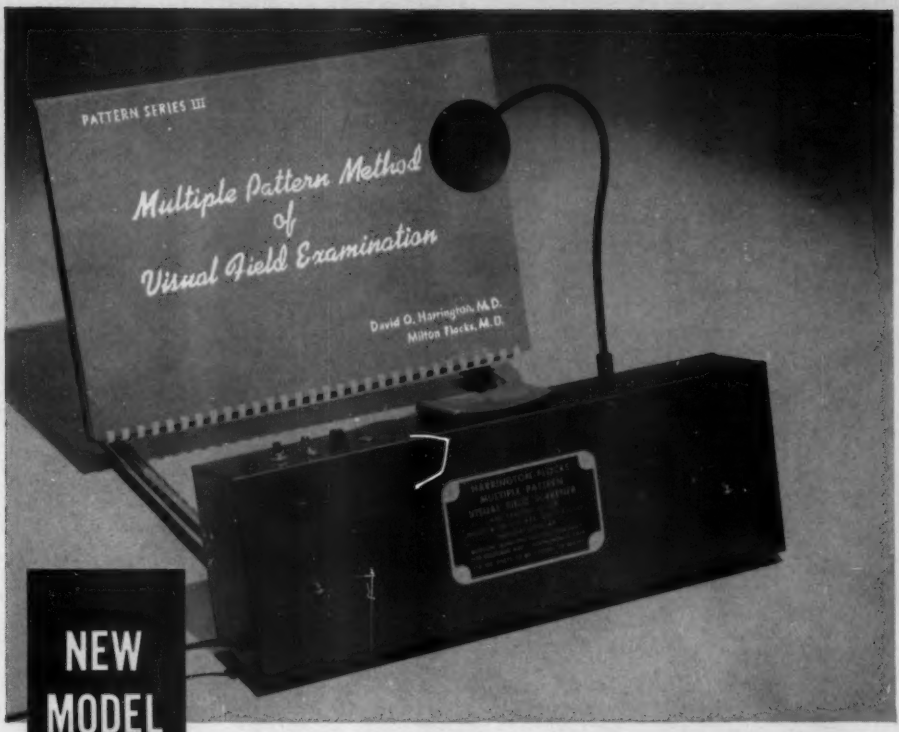

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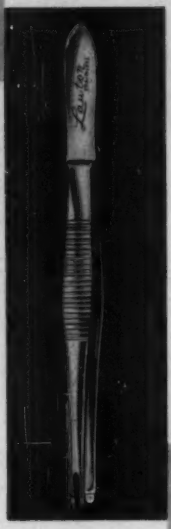

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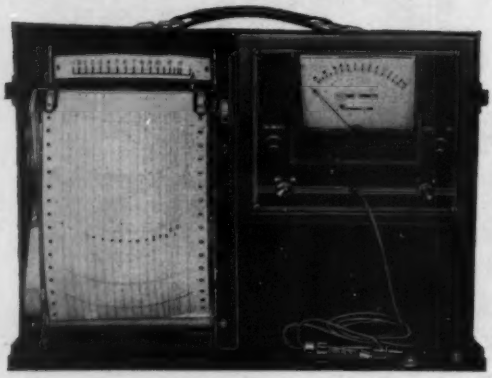

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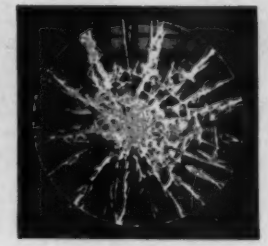

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